P. FALCIPARUM STRAIN RESISTANCE TO DRUGS. NEW DRUG TRIALS.

Jose Maria de SOUZA

INTRODUCTION

P. falciparum resistance to drugs worldwide and specially where endemic areas have been and are being detected, was first noticed in Brazil in 1910 when Artur Neiva reported the inefficiency of quinina to cure malaria infections\(^{15}\).

Later, mepacrine replaced quinine in malaria treatment, as this drug was feared more for its collateral effects than by the evidence of resistance to it by falciparum malaria parasites.

Mepacrine also caused many troubles and its use was discontinued only when chloroquine of the 4-aminoquinoline group was introduced, displaying a strong effect against all plasmodia responsible for human malaria.

In the mid-50’s, chloroquine that was developed during the II World War, started to be less effective against falciparum malaria parasites in the Guaporé territory (presently Rondônia state)\(^{5}\). Falciparum resistance to chloroquine appeared only a few years later in Colombia\(^{27}\).

Pyrimethamine used as an only drug to treat malaria was in a certain way discredited because of the resistance many falciparum strains showed to it. When it was used in adequate amounts associated to sulfamicid drugs though, it was effective to cure P. falciparum infections through a synergistic effect with potentiation of drug action\(^{26}\).

The 1970’s brought an increase in resistance to 4-aminoquinolines, chloroquine and amondiaquine as well as an increase in the development of parasite resistance to sulfadoxin and pyrimethamine, a phenomenon registered in Asia as well as in South America\(^{1,5,6,8,13}\).

Deterioration in efficiency of 4-aminoquinolines as well as of the combination sulphadoxin-pyrimethamine determined to resume the use of antibiotics in conjunction with quinine or in association with sulphadoxin-pyrimethamine; when these drugs were used without added antibiotics they had to be given for a longer period of time (7-10 days). Presently, the association of a 3-day dosis of quine plus sulphadoxin-pyrimethamine is ineffective towards many P. falciparum strains because of resistance.

The general outlook for the 1990’s is that as an efficient therapeutic program quinine is good when used for 7-10 days, the association of quinine (3 days) and tetracycline (7 days) and very especially a new synthetic drug, mefloquine that has proven usefull in areas of P. falciparum resistance in South America, Asia and Africa\(^{7,9,17,18,19,21,22}\).

A few cases have been reported in Brasil admitted as representing mefloquine resistance. Its assessment however will depend on a monitoring plan to clarify if we are dealing with a true resistance phenomenon or with some kind of inadequate cure from a partial drug clearance due to early vomiting, diarrhea or inappropriate intestinal absorption.

A MONITORING PLAN

The SUCAM’s Superintendência by means of its subdivisions of malaria (DIM) and of endemism control (DECEN) understanding the need to monitor the response of P. falciparum to anti-malarial drugs decided to ask several of its technical team (among those the author of this paper-JMS) to draw a report OF. SUCAM/DIM/BSB/nº1-645 (April 2, 1987) establishing norms for the development of a “Plan on surveillance of P. falciparum response to anti-malarial drugs in the Amazon region”.

Because of the great difficulties to implement the recommendations of the document, initially only in Belém and Marabá, Pará state and Goiânia, Goiás state was it possible to establish a monitoring for drugs used by SUCAM and more still for those associations of recent use: quinine (3 days) + tetracycline (7 days) and mefloquine (one single dosis).

In brief, it is necessary to point out that to reach the best results using the norms stated in the
"Plain on surveillance of *P. falciparum* response to anti-malarial drugs in the Amazon region" the following points should be followed:

1- a standard prescription sheet should be used where in one part the following should be recorded: patient identification, origin of infection, previous malaria history, present clinical picture, possible collateral effects due to medication and any pertinent observation. Elsewhere should be recorded: parasitemia (in mm$^3$), drugs used and dates when they were used; daily between days D0 and D7 (eight first days) and once every week on days D14, D21, D28, D35 and D42 and D63 on special cases.

2- In areas of highly active transmission (area II) control can be carried out more effectively between days D0 and D7 and to assure resistance evidence of RII and RIII intensity. Differentiation between S and R1 cases may be made occasionally.

3- In no-transmission or of low intensity areas (area I) control must be carried out between days D0 and D7 as well as up to D35 (on D42 in the case of sulphadoxin-pyrimethamine administration and D63 in the case of mefloquine) to uncover all variants of responses: S, RI, RII, RIII$^{16}$.

4- All responses to drugs routinely administered by SUCAM in all over the Amazon region which corresponded to therapeutic trials should be monitored.

SUCAM’s Regional Directory in Pará decided on a work strategy which though facilitating the plan operation did not mean significant change. So, a booklet was written to inform guards, inspectors and eventually technicians involved in the work; the booklet was also used by SUCAM’s Regional Directory in Goiás. The following rules were developed: SUCAM’s therapeutics was divided into levels of use according drug response, i.e., patients were first administered chloroquine, amodiaquine or sulphadoxin-pirimethamine association, by random allocation of 30 individuals into each group (or a multiple of 30). To be allocated into one of the groups patients could not present parasitemia higher than 50,000 asexual parasites/mm$^3$ of blood and/or a clinical picture of severe malaria characterized by intense dehydration, oliguria, obnubilation). A clinical picture as this is called a “first stage”.

In the case blood smears do not prove to be-
RESULTS AND COMMENTS

Analysis of results between July 1987 to December, 1988 showed that 4-aminoquinolines and the association sulphadoxin-pyrimethamine are effective for blood films negativation in more than 50% of patients the results being more effective in Marabá area where the percentage was as high as 70%. Nevertheless, the number of cases in need of another treatment series was also high. However, as the majority of cases resulted in a RI or RII resistance degree this means that was an effective mortality prevention.

Another aspect worthy of attention was that 4-aminoquinolines showed similar or better results than the association sulphadoxin-pyrimethamine suggesting that the use of this drug may be ruled out in face of a higher cost, risk of eliciting a hypersensitivity reaction and a greater facility to criate resistance in parasites.

Results from Goiânia, Goiás state, are similar to those in Pará; they show a higher index of cure by amodiaquine and a higher percentage of resistance (RI, RII and RIII) and inversely, negativity indexes were smaller than those found in Belém and Marabá areas.

Analysis of response to drugs of the second and third stages where a quinolinomethanol is always involved has shown that the negativity index is always greater than 90% reaching 100% when mefloquine is used; this means that no RII or RIII response was found in areas of Belém and Marabá except in very rare cases and even so there is doubt whether the dosage was adequate or losses occured due to vomiting and/or diarrhea.

For those cases where there was an observation period of at least 35 days it was possible to determine that whereas mefloquine was able to cure 100% of infections due to \textit{P. falciparum} resistant strains, quinine produced some RI resistance (relapse) possibly because of a greater difficulty to administer the drug for 10 days continuously.

When quinine was used for a short time (3 days) in association to tetracycline or sulphadoxin-pyrimethamine, in the first case failure was lower than 5% and close to 50% in the second case.

NEW TREATMENT TRIALS, NEW DRUGS

Genetic mutability of plasmodia has been shown through its great ability to induce resistance to different kinds of drugs regardless of its pharmacologic mechanisms. So, new drugs are necessary to promote a safe treatment of \textit{P. falciparum} malaria as a means for efficient, well tolerated drug trials of great operability different from what happens today as better tolerated drugs such as chloroquine have low efficiency although their use is operational. On the other hand, highly efficient drugs as quinine, have little tolerance and have low operability and finally, mefloquine which is highly efficient and operational but presents low tolerance and its pharmaco-kinetics favors resistance which must be avoided at all costs.

Among new anti-malarial drugs ready for use by humans is halofantrine, a fenathrene-methanol derivative and artemisinin, artemeter or artemunate, lactones, chemically sesquiterpen lactones with unusual endoperoxide linking.

Halofantrine is a drug already in use in Western Europe and Africa but has not yet been licensed in Brazil in spite of the large bibliography available. Artemisinin derivatives which studies on tolerance and toxicity were developed on the People’s Republic of China has recently been licensed by the Brazilian Ministry of Health.

Both halofantrine and artemisinin derivatives allow for recrudescence although this phenomenon is more frequent when the latter drug is used. Tolerance is good for both drugs and operability for its use is better for halofantrine than for artemisinin derivatives because the former is administered in three doses of 500mg per day (2 tablets every 8 hours) while artemisinin derivatives are injected for 5 days (artemeter) or for 6 days or, one tablet/12 hours per os (artesunate). The great advantage of the Chinese drug would be the availability of a formulation to be administered intravenously for 2 days (freeze-dried artemunate) in cerebral malaria cases.

Soon to be available is the possibility of removal of \textit{P. falciparum} resistance to chloroquine through the association of this drug to blocking agents of Calcium channels (verapanil) and/or tricyclic anti-depressants which seem to have greater activity than the former.
Research on artemisinin derivatives and the need to understand its action mechanisms led to the synthesis of trioxan, tetroxan and peroxide derivatives also possessing antimalarial activity as it is the case with Yingzhaosu A, a sesquiterpen peroxide extracted form Artabotrus uncinatus\textsuperscript{10,12}.

Bases possessing special properties as pironaridine, also synthesized by the Chinese, have shown an extraordinary schizonticide activity for rodent and monkey malaria. Many basic studies have been carried out with this drug since its synthesis occurred in 1970\textsuperscript{10}.

One more drug object of synthesis by the Chinese is benflumetol, already licensed as an antimalarial drug in the People’s Republic of China where it is used orally associated to artemeter for \textit{P. falciparum} infections. The majority of information regarding this drug is extracted from studies conducted in the People’s Republic of China and so, it is necessary for the Western world to conduct studies of its own in order to assess its usefulness.

Several other anti-malarial drugs possessing activity directed towards forms inside red blood cell (hydroxypiperaquin) or to tissue forms (WF 238.605) are under study and some of them have been object of extensive pre-clinical trials and have even been used in experimental human malaria cases as pyridinomethanol (WR 180.409).

As far as we can see there is urgent need to constitute a Multicentrical Investigative Center in Brazil approved by the Ministry of Health in order to make uniform research of new anti-malarial drugs in this country as well as other anti-parasite drugs. This would bring advantages to users as well as avoid strain between research conducted in different regions of the country, once scientists from research institutes and Universities in the Amazon region are the ones who live with the everyday reality of patients and the disease but researchers from the South an Southeast are the ones who receive the largest sum from granting agencies.

Multicentral investigations on mefloquine in Brazil, as part of the International Centers for Clinical-Pharmacological Research Program have shown the potential Brazil has to conduct trials on new drugs well within the demands of clinical pharmacological research including those of an ethical nature by means of local Ethics Committee which very vigourously examine the adherence of the protocol to the charters of Helsinqui, Tokio and Venice\textsuperscript{18,19,20,21,22,24,28}.

In Brazil legislation regarding medical research is ruled by Resolution 01/88 from the National Health Committee, which competence derives from decree 93,933 of January 14, 1987 and from the Medical Ethics Code of the Brazilian Federal Medical Committee, besides penal and civil law responsibilities.

Careful reading of the above mentioned medical by-laws shows that they bear a certain disagreement: while Art. 7, of resolution 01/88 considers that medical research has different levels of risk, and Art. 13 states that the Ethics committee may allow for an informed consent to be given orally in cases of minimum risk research (a very frequent case), the Medical Ethics code rules out such possibility, which sometimes may go against the interests of a community, concerning minimum risk drug research based on international literature.

\textit{P. falciparum} strains highly resistant to 4-aminquinolines and to antifolics, presenting as well somewhat of resistance to other anti-malarial drugs as quinolinomethanols and antibiotics are a matter of great worry to Brazilian Ministry of Health personnel. So much so that they decided to accept previous research done by Chinese investigators on artemisinine derivatives as worthy of licence in all of the Brazilian area as anti-malarial drugs.

I do not know of previous consultations to any group of investigators on the use of antiparasitic drugs to serve as a basis to support the decision of the Ministry of Health of licensing the derivatives artemeter and artesunate administered orally or intravenously, although I believe such consultation was done. Anyway, what seems to me of most importance is that a permanent body of researchers on the investigation and use of antiparasitic drugs and especially anti-malarial drugs be established. This group should be constituted by names chosen by Universities, research institutes and scientific societies for evaluation and confirmation by the Brazilian Ministry of Health.

If this were the case, the withdrawal of highly important drugs would have been avoided such as clindamicin, a highly effective antibiotic for the treatment of falciparum resistant malaria, well tol-
erated by malarious pregnant women; or still, that halofantrine would have to wait so long to be licensed by the Ministry of Health in spite availability of data showing it to be a safe drug, well tolerated and highly effective towards falciparum malaria in distant places where medical help is precarious.

These points seem important to be discussed in the seminar so we may provide the authorities and to society with our contribution to what is written in the Brazilian constitution: "health is a right of all citizens and a duty of the State".

**CONCLUSIONS**

1- In spite of a high resistance to 4-aminoquinolines these drugs are still very important for morbidity control and mortality prevention by *P. falciparum* infections.

2- The association sulfadoxin + pyrimethamine should no longer be used alone (is no better than the 4-aminoquinolines) or associated to quinine as it allows for high percentage of recrudescence.

3- The administration of 3 day-quinine + 7-day tetracycline seems to be an excellent combination for treatment of *P. falciparum* cases resistant to 4-aminoquinolines and to sulfadoxin + pyrimethamine.

4- Administration of quinine for 10 days although with its low operability cures a high proportion of cases and therefore may be used as a second alternative to malaria resistance cases.

5- Mefloquine is still 100% efficient to cure resistant malaria infections but its use should be restricted.

6- Therapeutic trials with new drugs and/or new association of drugs are urgent and evaluation requires research personnel to be trained to administer it.

7- Ethical information concerning medical research needs to be made available to clinicians and researchers so they may dispense a high quality of medical care to the individual and the community.

**SUGGESTIONS**

a- To suspend the use of the association sulfadoxin + pyrimethamine in high transmission areas for a long time in order to decrease the effect of the drug on the parasites what may restore the quality of the response to the association quinine + sulfadoxin + pyrimethamine.

b- To continue with the use of chloroquine and amodiaquine with a severe control of its dispensing in order to facilitate the analysis of monitoring results.

c- To use quinine alone or associated to tetracycline to solve less severe cases of resistance to 4-aminoquinolines.

d- To restrict the use of mefloquine in endemic areas as much as possible and use it in 5% or less of all cases.

e- To supervise the illegal use of mefloquine and other anti-malarial drugs by businesses or individuals which buy it abroad or from non-licensed dealers.

f- Stimulate monitoring of undesirable effects of drugs in order to better evaluate its risk/benefit ratio.

g- Create a group to act as experts of the Ministry of Health on decisions regarding withdrawal or licensing of new anti-malarial drugs in Brazil.

**REFERENCES**


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