RESPONSE OF PLASMODIUM FALCIPARUM TO CHLOROQUINE IN HOSPITALIZED PATIENTS AT SIDAMO REGIONAL HOSPITAL

Wondwossen Desta*,MD & Yohannes Gebrat**,MD

ABSTRACT: The response of p.falciparum to a standard regimen of chloroquine (25 mg/kg body weight) was studied in 38 patients (27 males, 11 females) hospitalized at Sidamo regional hospital, Yirgalem, southern Ethiopia. Resistance occurred in 44.7% of the patients, 64.7% RI, 5.9% RII and 28.4% RIII. Resistance rates were highest (75%) in children below 9 years of age. Of those resistant to chloroquine all except one showed clearance of parasitemia and clinical cure after Quinine or Sulfadoxine pyreimetnamine (Fansidar). This study has confirmed the presence of chloroquine resistant strains of p.falciparum in the area. It is recommended that additional in vitro and in vivo studies should be done in order to rationalize the use of alternate drugs like Quinine more economically.

INTRODUCTION

P.falciparum resistance to chloroquine has been increasingly reported from all over the world. The first reports were simultaneously published independently from Thailand in 1962, Venezuela in 1960 and in Colombia 1960 (1). The first confirmed African cases were found in Tanzania (2) and Kenya (3) approximately 10 years ago. There have been studies completed in Ethiopia, Nazareth town (4) and Addis Ababa (5,6) and in both resistance was found.

The present study was undertaken to identify the existence of p.falciparum resistance to chloroquine which was suspected following an observed mortality rate in patients taking chloroquine at Sidamo regional hospital. We considered chloroquine resistance to p.falciparum as one of the potential factors for failure of response to treatment and consequent increase in mortality.

PATIENTS AND METHODS

This study was conducted from July 8 to August 8, 1988 at Sidamo regional hospital, 120 beds, located 317 km south of the capital Addis Ababa. A total of >150 patients presented to the hospital with fever during the study period. The following inclusion and exclusion criteria were used.

Inclusion criteria were a smear positive for p.falciparum, any age, willingness to stay 8 days in the hospital giving blood for examination daily.

Exclusion criteria included a positive Dill Glasco test, very low (<1000/cm^3) or very high (>100000/-cm^3) parasite counts, pregnant women.

42 patients fit the study criteria of which 4 were excluded during 7 days follow up (2 vomited the drug, 2 missed follow up). 38 patients were successfully followed up and reported here.

---

*Medical Department, Medical Faculty, Addis Ababa University
**Sidamo Regional Hospital

Considering the first as day 0 blood smear is taken daily from each patient up to day 7. Smears (thin and thick) from each patient were stained with Giemsa 3% for 15 minutes. Parasite counts of thick smear per 300 Leucocytes were made by 2 separate individuals, experienced microscopists and the average is recorded after being multiplied by a factor of 20 taking 6000 WBC per mm^3 as a normal average count.

Chloroquine phosphate tablets (Ephraim) Batch No.509122.1 with 150 mg base were used. Each patient received a total of 25 mg base/kg in three divided doses orally (10 mg/kg on day 0, 10 mg/kg on day 1, and 5 mg/kg on day 2) (8). The dose used is higher particularly in children where difficulties arise in dividing tablets

and syrups. The intermuscular route has been used in two patients. Injection was followed by oral tablets. Chloroquine absorption was checked by Dill and Glazco (DG) tests of urine in the first three consecutive days.

Frequent visits of patients were made to insure drug ingestion, and to exclude patients who vomited the drug in the first three days of hospitalization. Alternate drugs, Quinine 25 mg/kg daily for 10 days or Fansidar (525 mg tablets) half to three tablets according to age difference once orally were given to patients who failed to clear parasitologically or deteriorated clinically.

RESULTS

38 patients completed the 7 day study in the hospital. Parasitemia cleared in 21 (55.3%) patients. This makes the rest 17 (44.7%) patients resistant (Table 1). The mean parasite density index (10) calculated from table 1 is 7.30. No correlation was seen between the level of parasitemia and the clearance rate time. This is best exemplified by case No.31 who had very high count on day 0 but showed progressive and rapid clearance in contrast to case No.6 who presented with low count but failed to clear later. Many of the patients showed day to day fluctuation of parasite count (Table I). Of the resistant cases 11 (64.7%) patients showed resistant at RI level, 1 (5.9%) at RII and 5 (29.4%) at RIII levels (Figure 1). The youngest patient was one year old and oldest 70 years old. The highest resistance rate recorded was in those less than 9 years of age and no resistance was noted above the age of 50 years.

DISCUSSION

This study as in other in vivo studies tried to adhere to the WHO standard 7 day test (8). The resulting 44.4% resistance at various levels may seem high but was expected considering the treatment failures and deaths we had recently encountered in patients receiving chloroquine. The resistance rate would have been even higher if the follow up had been extended up to 28 days. Comparable hospital study in Tanzania (8) revealed 46.2% resistance, while 22 of 98 patients (22.4%) resistance was reported from an Ethiopian (5) in vivo field study. Hospital base studies show higher resistance rates. One explanation for this could be patients in the former group come from the community where self medication and under dosage is widely practised resulting in intense drug pressure and emergence of resistant strains.

The majority of our patients are RI (64.7%) and only a few patients are RII and RIII (35.3%). This resembled the Ethiopian study (5) which showed 63.6% RI versus 36.4% RII plus RIII and contrasts to the Tanzanian study (5). 7.7% RI versus 92.3% RII plus RIII. The high RI level of resistance in our study may indicate a better response of parasites to chloroquine, but on the other hand makes the follow up of patients difficult i.e. in RI parasitemia clears rapidly in few days but recrudescence occurs later while patients are at home where as in RII and RIII patients can be recognized earlier with clinical follow up and examination of blood smears.

Analysis of resistance in terms of age shows that three fourths of the patients below 9 years are resistant and almost all patients above 50 years of age are sensitive. The difference in immunity between adults and children has been suggested to explain this (9).

All cases resistant to chloroquine showed clearance after Quinine or Fansidar in an average of 2 days following the start of the treatment. We used Fansidar in the minority when we did not have Quinine. Both drugs are well tolerated and we have not seen major side effects except headache and transient loss of hearing and tinnitus in some. Case No.32 died despite Fansidar which was started on day 3. Quinine which is preferred in a comatose patient i.e.

Table 1. P.falciparum Response to Chloroquine in Vivo WHO 7-Day Test. (Mean of 6000 Leucocytes/mm^3)

Patients Serial No.	No. of Trophozites/mm^3 on Day								Classification of
	0	1	2	3	4	5	6	7	
1	>100000	7720	0	0	0	0	1180	3340	RI
2	46000	53360	90000	10650	16800	18360	Lost	8100	RIII
3	7200	6000	4000	5300	3000	0	0	0	S
4	Lost	600	0	0	0	0	0	0	S
5	1280	880	2360	Lost	24000	0	19920	2880	RI
6	7100	2860	9120	2280	16500	4200	4760	5820	RIII
7	48700	23400	20880	4160	10920	10180	5660	4160	RIII
8	22560	Lost	7120	0	0	0	0	3120	RI
9	17640	0	0	0	0	0	0	0	S
10	3200	0	0	0	0	0	0	900	S
11	>100000	20300	0	0	0	0	0	0	RI
12	5700	11700	0	0	0	0	0	0	S
13	1800	480	0	0	0	0	0	0	S
14	13400	6720	9820	6000	1500	4100	2320	5260	RI
15	2820	0	5940	0	0	0	0	0	S
16	7800	1020	680	0	0	960	0	0	S
17	15480	21920	27340	0	0	0	0	1560	RIII
18	2320	1760	600	900	0	0	0	0	S
19	2300	1320	0	720	200	400	0	0	S
20	22560	19600	16800	9840	4640	3080	880	0	S
21	100000	2760	8400	1320	0	0	0	0	S
22	21360	4860	4600	0	0	0	0	19200	RI
23	1100	1440	0	500	0	0	9400	540	RI
24	14400	10660	2160	1360	0	0	0	1380	RI
25	3900	0	0	0	0	0	460	340	RI
26	600	520	0	0	0	0	0	0	S
27	2700	0	0	0	0	0	0	0	S
28	500	360	100	0	200	0	0	760	RI
29	2100	0	0	0	0	0	0	0	S
30	2960	Lost	800	0	2480	0	0	320	RII
31	100000	12720	0	0	0	0	0	0	S
32	100000	>100000	90000	44600	50000	Exp	-	-	RIII
33	47300	14160	10440	5160	13000	1220	Lost	600	RII
34	1700	1280	0	0	0	0	0	0	S
35	1200	0	0	0	0	0	0	0	S
36	3740	640	0	0	0	0	0	0	S
37	8420	2040	5680	0	1700	0	0	0	S
38	2920	100	600	Lost	580	1220	1120	0	S

cerebral malaria (1) was not available at that time.

In summary, we know that chloroquine, still the drug of choice is widely used at all level of health institutions in the area for proved or some times suspicious cases of malaria. Little follow up of ambulatory patients is seen unless they come by themselves with reinfection or recrudescence. Though we agree that over use or misuse of other drugs should be avoided (11) supply of drugs besides chloroquine should be available at least to the hospitals.

In areas like Sidamo increased awareness of the problem by health personnel, follow up blood smears at least on day 3, 7 and 28 (in order to act appropriately) may be mandatory. Finally we recommend further in vivo and in vitro studies here and in other parts of the country so as to have uniform and proper use of alternate drugs like quinine.

ACKNOWLEDGMENT

We are indeed grateful to Dr. Sigmund Lende (former Medical Director of the hospital) for his continuous encouragement and advice. We are also in debt to Dr. Karl Roth Medical Director of the hospital for reviewing the manuscript and financial support. Our thanks go to Dr.Tedbabe Degife, Dr. Tenbit G.Tsadik, Dr. Beede Lemma, Dr. Tesfaye Kassa, Dr. Einar Eriksen, Ato Ephrem Olane for their continuous assistance by referring patients to us and for their heartly collaboration throughout the study. We are also grateful to W/o Aynalem and Ato Assefa (microscopists) for their help in counting the slides. Finally we thank W/o Wubit T.Mariam for her secretarial services.

REFERENCES

1. G.T. Strickland. Clinics in Tropical Medicine and Communicable diseases Malaria. April 1986.
2. Campbell, CCchin, W. Collins, WE, Teurschk S.M and Moss, D.M. Chloroquine Resistant P.falciparum from East Africa: Cultivation and drug sensitivity of Tanzanian 1/CDC Strain from and American Tourist. *Lancet.* 1979. 11: 1151-1154.
3. FOgh, S. Gepseu, Siand Effe ose, P. Chloroquine resistant P.falciparum malaria in Kenya. *Trans R. Soc. Trop. Med Hyg.* 1979. 73: 228-229.
4. Nigussie, Gabre Mariam, Yahya, Abdulahi and Assefa Mebrate. Preliminary studies on responses of P.falciparum to chloroquine in Nazareth Town, central Ethiopia. *Ethiop. Med. J.* 1982. 25, 209.
5. Teklehaimanot - A 1986 Chloroquine Resistant P.falciparum malaria in Ethiopia. *Lancet.* 2: 127-129.
6. Tsehay-Assefa. A case of plasmodium falciparum infection resistant to chloroquine. *Ethiop. Med. J.* 1987. 25, 209.
7. Lelijveld, J. and Kortman, H. The Eosin test of Dill and Glazko. *Bul. Wld. Hlth. Org.* 1970. 42, 477.
8. Advances in malaria chemotherapy. Report of WHO Scientific Group. WHO Geneva. 1984.
9. T.K. Mutabingwa, E. Hills, W.L. Kilama. Response of P.falciparum in hospital patients at Mugeza, Tanzania. *E. Afr. Med. J.* 1985. 62 No.3: 161-170.
10. Bruce-Chwatt, L.T. Parasite density index in malaria. *Trans. Roy. Soc. Trop. Med. Hyg.* 1958. 52, 398.
11. Malaria control as part of primary health care. Report of a WHO study group . *Technical Report Series.* WHO Geneva. 1984.