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CHLOROQUINE-RESISTANT PLASMODIUM FALCIPARUM

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ABSTRACT... Objective: The study was conducted to determine the frequency of Chloroquine-resistant Plasmodium falciparum. **Subjects & Methods:** This was a descriptive case series study conducted at Muhammad Medical College Mirpurkhas & Liaquat University Hospital Hyderabad/ Jamshoro, from January 2007 to December 2007. Total 160 patients with acute attack of fever were selected & studied who fulfilled the inclusion criteria. The WHO extended test was done by giving 25 mg/kg body weight of Chloroquine base over 3 days. The interpretation of the test was done as per criteria laid down by WHO. **Results:** Out of one hundred sixty, 110 (68.75%) were males and 50 (31.25%) were females with ratio of 2.2:1. The age range 16-45 years with mean 28±12 years. Seventy one patients (44.375%) were Chloroquine sensitive. Chloroquine-resistance (CQR) RI, RII & both RI RII noted were 28.125%, 15.645% & 43.75% respectively. The CQR- R III was not observed in our study. **Conclusions:** In view of this situation, more organized and thorough studies must be conducted to elucidate the epidemiology, geographic-distribution & degree of Chloroquine resistance. And the local strategies be made to overcome this problem and to assess the need for changing the first line drug.

Key words: Malaria, Plasmodium falciparum, Chloroquine resistance.

INTRODUCTION

Malaria is present in endemic form in about 103 countries of the world[1]. More than 2 billion people around the world are at risk for malaria infection. The estimated annual global incidence of malaria is 300-500 million cases and about 20 million deaths occur worldwide each year[2]. In Pakistan, half a million-malaria cases occur annually and Sindh and Balochistan are more affected provinces. Malaria is cause of estimated fifty thousand deaths each year mostly in infants, children and pregnant women. Hence, malaria is a major public health problem of this country, which threatens millions of people[3]. This higher mortality is due to lack of awareness and application of malaria case management guidelines in high-risk severe and complicated falciparum malaria[4]. Malaria endemic regions are some of the world's most impoverished areas where plasmodium falciparum is responsible mainly for deaths.

Hence, one reason for the below poverty indicators of Sindh and Balochistan especially in their coastal, remote and arid districts can be high annual parasite incidence in these areas[5]. Annual parasite incidence and plasmodium falciparum ratio in Sindh are increasing as reported in year 2004[6].

In the last decade there has been a six fold increase in P.falciparum malaria, which now comprises 42% of all

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malaria cases recorded by the National Malaria Control Programme[7]. Resistance among P.falciparum is more common, particularly in malaria endemic countries. Pakistan, one of the five countries with moderate endemecity is also facing this problem. (Ram et all 1997)[8]. Until the end of the 1980s, most in vivo studies focused on the parasitological response to a given drug, and infections were classified as sensitive (S), or resistant (R) at one of three levels, RI, RII or RIII.

RI: Response corresponds to an initial clearance of parasitaemia and then recrudescence 08 or more days after treatment.

RII: Response is the clearance or substantial reduction of parasitaemia with recrudescence of parasitaemia on day 7.

RIII: Response refers to a situation in which there is no initial reduction of asexual parasitaemia and the levels may actually increase[9].

In Pakistan, the estimated in-vitro resistance of P.falciparum to one or more antimalarial drugs is about 40%. In some regions, Chloroquine resistance to P.falciparum ranges from 18-62%[2]. This alarming situation compelled us to conduct a study in our institutes to determine the response of P.falciparum to a standard dose of chloroquine.

MATERIAL & METHODS

The study was conducted at Department of Medicine, Muhammad Medical College Hospital Mirpurkhas & Liaquat University Hospital Hyderabad/Jamshoro from January 2007 to December 2007. A total of 160 patients were selected through probability purposive sample. The data was collected on a structured proforma. The inclusion criteria was: i) single species infection; plasmodium falciparum; the ring and trophozoites ii) a minimum threshold of 1,000 sexual parasites but <80,000 asexual parasites per cubic millimeter of blood; iii) the patient had not received any of the following anti-malarial drugs for the specified period: 4 aminoquinolines (Chloroquine) (14 days), sulfadoxine-pyrimethamine (fansidar) (4 weeks), and mefloquine (6 weeks). The WHO in vivo test was used for studying the problem of Chloroquine resistance in malaria. The patients with acute attack of fever were selected for the test. The WHO extended test was done by giving 25 mg/kg body weight of Chloroquine base over 3 days. The interpretation of the test was done as per criteria laid down by WHO[10]. During the follow-up stage, blood slides of all subjects recruited were obtained on days 1,2,3,7,14,21,28 for monitoring the course of asexual parasitaemia (Rowland et al, 1997). Once the resistance of RII and RIII was established, patients were withdrawn from the study and treated with alternative anti-malarial drugs. The comparisons of difference in the means were calculated by student's t-test. P-value of <0.05 was taken as significant for all statistical analysis.

RESULTS

One hundred & sixty patients were studied according to inclusion criteria. Out of these 110 (68.75%) were males and 50 (31.25%) were females. The male to female ratio was 2.2:1. The age range was 16-45 years, mean 28±12 years. The parasite clearance was compared and analyzed for the sensitivity and resistance. Seventy one patients (44.375%) became afebrile on day 5th and blood films were free of malaria-parasite, so all these patients were Chloroquine sensitive. Chloroquine-resistance (CQR) RI was noted in 64 (28.125%) patients (p=0.003), they responded well, became afebrile but parasite clearance was partial and on day 10th follow-up all these patients were running fever and blood films were positive for the malaria-parasite. CQR- RII was noted in 25 (15.625%) cases (p=0.002) & there was substantial reduction of parasitaemia with recrudence on day 7th, shown in (Table I). In our study CQR- R III was not observed. Regarding other parameters hemoglobin values < 10g/µL were noted in 60 (37.5%), leukocytes ≥12000 /µl in 117 (73.125%) patients while Bilirubin ≥ 2 were observed in 64 (40%) patients. Hypoglycemia was seen in 93 (58.125%) while sixteen (10%) patients were having Creatinine ≥ 2 (Table- II). Fever, nausea & vomiting, diarrhea, dark colour urine, hepatomegaly, splenomegaly, and jaundice were noted (Table -III).

Table-I. Chloroquine Sensitivity Resistance (n=160)		
Response level	**No. Patients**	**%**
S	71	44.375%
RI	64	28.125%
RII	25	15.625%
RIII	0	0

Table-II. Laboratory Results (n=160)		
Symptoms	**No. Patients**	**%**
Hemoglobin < 10 ≥10	 60 100	 37.5% 62.5%
Leukocytosis < 12000 (per µl) ≥ 12000 (per µl)	 43 117	 26.875% 73.125%
Bilirubin < 2 ≥ 2	 96 64	 60% 40%
Blood glucose level < 100 ≥ 100	 93 67	 58.125% 41.875%
S. Creatinine ≥ 2	 16	 10%

Table-III. Miscellaneous signs and symptoms (n=160)		
Symptoms	**No. Patients**	**%**
Fever < 103 ^{O}F ≥ 103 ^{O}F	 43 117	 26.87% 73.125%
Nausea & Vomiting	93	58.125%
Diarrhea	20	12.5%
Dark/Black colour urine	70	43.75%
Splenomegaly	36	22.5%
Hepatomegaly	23	14.375%
Jaundice (Clinically)	45	28.125%
Hypotension (Systolic BP < 100mmHg)	60	37.5%

DISCUSSION

Despite decreased sensitivity Chloroquine continues to be the drug of choice for the treatment of malaria in Pakistan. The results of our study showed Chloroquine-resistance (CQR) RI, RII & both RI RII of 28.125%, 15.645% & 43.75% respectively. The RIII was not seen in our patients. CQR has been reported in Afghan refugees which showed RI and RII of 68% & 2% respectively. In one study from Faisalabad 8 RI, RII of 54.5% & 15.1% were noted respectively. According to survey conducted by Shah et al[11], showed a frequency of RI & R II of 30 - 84% & 2 - 36% respectively. Our results of CQR, (both RI & RII) of 43.75% are comparable with the above mentioned studies. Our results are also similar to Bhalli et al[12], Iqbal et al[13], & Khichi et al[14] which showed CQR of 33%, 39.9%, & 26.66—33.65% respectively. One study from Assam has shown results of CQR of 30.4%[15] which also comparable with our results. The results of one in-vivo study from Iran[16] performed on 1301 patients during 1990-1996 showed that 890 cases (68.4%) were having CQR. Another in-vivo study on antimalarial drugs efficacy carried out around the same period of time revealed 78.5% CQR with 17.4% of early treatment failure, 34.7% of late clinical failure and 26.4% of late parasitological failure[16]. One study from India has shown R I, RII and R III of 54%, 5%, 3.6% respectively[17]. Our results are comparable with these studies too. The increasing prevalence of CQR P. falciparum worldwide has serious public health implications for poor countries like Pakistan. In most of sub-sahran Africa and Asia, CQR is a huge problem, accounting for more than 90% of malaria cases in parts of West Africa and south-east Asia, including Thailand. In Pakistan, the estimated in-vitro resistance of P. falciparum to one or more antimalarial drugs is about 40%. In some regions, CQR to P. falciparum ranges from 18-62%[2].

CONCLUSIONS

The chloroquine resistance of 43.75% in this study reveals an alarming situation. In view of this situation, more organized and thorough studies must be conducted to elucidate the epidemiology, geographic-distribution &

degree of Chloroquine resistance. And the local strategies be made to overcome this problem and to assess the need for changing the first line drug.

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