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Relapse Rate of Vivax Malaria with Different Regimens of Antirelapse Treatment in Iran: A Field Evaluation

[1]Masoud Salehi and [2]Fatemeh Rakhshani

In this study shorter duration of antirelapse therapy was compared to that of 8 weeks regimen. In 1998 and 1999 antirelapse therapy of vivax in Sistan and Baluchestan province in southeast of Iran was done with different regimens according to manpower and executive facilities. A cohort study was compared clinically and parasitological relapse of vivax malaria in 200 patients with one-week therapy, 200 patients with 2 weeks, 800 patients with 4 weeks and 500 patients with 8 weeks therapy by primaquine. Relapse rates of vivax malaria by each regimen were 23.8, 13.2, 5.4 and 4.6%, respectively. Relative risk of relapse in comparison with 8 weeks regimen was 5.2, 2.9 and 1.2, respectively. Number Need to Harm (NNH) was 5, 12 and 125. Interval of the first relapse varied between 6 to 52 weeks with the mean of 28.8 weeks (CI 95%: 24.2-33.1). The relapse rate was not different between men and women. The relapse rate by 4 and 8 weeks regimes were low and there was not significant difference of relapse rate in 4 and 8 weeks regimes. It is recommended to use 4 weeks therapy instead of 8 weeks therapy in special situations.

Key words: Malaria, *Plasmodium vivax,* relapse, treatment

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For further information about this article or if you need reprints, please contact:

Masoud Salehi
Bio-Ali Hospital
Shariati Street
Zahedan, Iran

Tel: +98 5413228101-2
E-mail: shahstan@yahoo.com

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[1]Department of Tropical and Infectious Disease, Faculty of Medicine, Zahedan University of Medical Sciences and Health Services, Iran
[2]Faculty of Public Health, Zahedan University of Medical Sciences and Health Services, Iran

INTRODUCTION

Malaria is one of the most important health problems in southeast of Iran particularly in Sistan and Baluchestan province. In the last decade about 20-100 thousands malaria cases have occurred every year in the country. Over 50% of which was happened in Sistan and Baluchestan province, two-third of the cases were caused by *Plasmodium vivax*[1].

Primaquine is the only drug available that enable eliminate hypnozoites from the liver and prevent relapses of vivax malaria. There are variations among different strains of *P.vivax* in terms of sensitivity to the primaquine treatment and the rate of relapse[2]. The WHO has recommended a treatment of either 15 mg per day of primaquine for 14 days or 45 mg weekly for 8 weeks[3]. There is some evidence that the vivax malaria in Indian subcontinent showed a higher sensitivity to primaquine action and may respond to a 5-day treatment of 15 mg per day.

Because of a high prevalence of G6PD deficiency in our country that promotes hemolysis as a consequence of daily treatment with primaquine, an intermittent treatment regimen of 0.75 mg of base per kg (45 mg for adult dose) for 8 weeks is preferred. The incidence of side effects is lower with weekly, compared to daily dosages.

Drug therapy of malaria in Iran is supervised by health care workers, so weekly therapy necessitating several additional visits to the patient's houses, which mostly are quite remote. This strategy is expensive and creates enormous operational difficulties for malaria control programs. In addition, the effectiveness of this regimen on prevention of vivax malaria relapse in this area has not been evaluated. On the other hand, WHO and most of the experts believe that antirelapse treatment should be restricted to the low transmission areas and where the malaria transmission dose not occurs[3].

It was also found that the effect of antirelapse treatment depends on total dose of primaquine rather than duration of treatment[4]. In another study a one-day regimen of primaquine showed a significant reduction in the frequency of recurrent *P.vivax* parasitemia comparing it to amodiaquine alone over a 9 month follow up period[5].

This study was designed to compare the effectiveness of different regimens of primaquine including one, two, four and eight-week treatment on prevention of vivax malaria relapse.

MATERIALS AND METHODS

Antirelapse treatment of vivax malaria has been performed in Sistan and Baluchestan province, southeast of Iran since 1997 with different regimens of primaquine according to manpower and executive facilities. A cohort study was designed to determine and compare the rate of relapse following treatment with different regimens, 200 cases for 1-week, 200 for 2-week, 800 for 4-week and 500 for 8-week intermittent therapy (each week 0.75 mg of primaquine per kg up to 45 mg). They were followed up for one year after the initial treatment since June 1998. The study cases were randomly selected from vivax malaria patients settled in four districts located in Sistan and Baluchestan province including Saravan, Iranshahr, Nikshahr and Chabahar. The Annual Parasite Incidence of malaria (API) during the time of study was about 20-25 per 1000 of population. The sample was selected among patients who had not been abroad at least for a year, had not mixed infection and had no experience of malaria infection during past three years. In addition, they have received initial treatment correctly. The pregnant patients and children below 1 year were excluded. Primaquine phosphate was purchased from the Pars-Daroo Company, Tehran, Iran and the drug was administered under supervision of health-care workers.

The patients were monitored for one year after the primary treatment. They were visited monthly by health care workers and blood smears for parasite investigation were prepared for those who revealed clinical symptom, i.e. fever. In case of malaria relapse, the same drug regimen as in the primary treatment was applied. Patients, who moved away or were unavailable during the one-year follow-up, were excluded from the study. A questionnaire was also completed for every individual. Normally distributed interval data were analyzed using student t-test or ANOVA. Nominal data were analyzed using Pearson's χ^2 test. The hypothesis of equality of means discarded when the probability (P) of a type I error was =5%. The data were analyzed with SPSS statistical software (SPSS, Chicago, IL). Relative Risk (RR), Absolute Risk Increase (ARI), Number Needed to Harm (NNH) for each regimen was compared to 8-week regimen.

RESULTS

A total of 1700 malaria patients were subjected to the study, being distributed to 4 different regimens of antirelapse primaquine therapy. We succeeded to follow up 1501 cases out of 1700. They included 64.6% males and 35.4% females, aging between 1 to 70 years with an average of 19.6 years. The characteristics of patients are summarized in Table 1.

The relapse rates, with 1, 2, 4 and 8-week regimens were 23.8, 13.2, 5.4, 4.6%, respectively. No difference in the rate of relapse was observed between male and female ($p = 0.48$). Also the age groups did not show significant

Table 1: The characteristics of patients at different regimens

Duration of treatment	One-week	Two-week	Four-week	Eight-week
The number of initial patients	200.0	200.0	800.0	500.0
The number of patient with one-year follow up	172.0	174.0	721.0	434.0
% Male sex (total)	68.0	75.9	57.7	70.0
The patients without relapse	68.7	74.8	57.7	71.0
The patients with relapse	65.9	82.6	69.2	50.0
Mean of age (Years)	20.5	17.6	20.4	19.4
(CI 95%)	(18.2-22.8)	(15.5-19.6)	(19.3-21.6)	(18.7-20.3)
The patients without relapse	21.0	17.2	20.4	19.4
	(18.2-23.7)	(15.5-19.3)	(19.2-21.5)	(17.0-19.7)
The patients with relapse	19.0	19.9	21.5	23.0
	(14.7-23.2)	(13.1-26.7)	(16.5-26.5)	(14.0-32.4)
The number of relapse(patients)				
One	41.0	23.0	39.0	20.0
Two	4.0	1.0	6.0	4.0
Three or more	1.0	0.0	3.0	0.0
Relapse Rate (%)	23.8	13.2	5.4	4.6
(CI 95%)	(17.3-30.3)	(8.1-18.3)	(3.7-7.1)	(2.6-6.6)
Mean of first interval relapse (week)	29.9	32.4	23.0	33.6
(CI 95%)	(25.6-34.1)	(26.7-38.1)	(18.1-27.8)	(27.8-39.4)

Table 2: The results of antirelapse therapy with different regimens of primaquine

Treatment regimens	Relapse rate	RR*	ARI**	NNH§
1-week (n=172)	23.8	5.2	19.2	5
2-week (n=174)	13.2	2.9	8.6	12
4-week (n=721)	5.4	1.2	0.8	125
8-week (n=434)	4.6	-	-	-

* Relative Risk; ** Absolute Risk Increase; § Number needed to harm

differences in the relapse rate. The relapses appeared 6 to 52 weeks following the initial treatments with an average of 28.8 weeks for the first time relapses. Other findings including the values of Relative Risk (RR), Absolute Risk Increases (ARI) and Numbers Needed to Harm (NNH) are comparatively summarized in Table 2.

DISCUSSION

The present study showed that antirelapse therapy of vivax malaria using 1-week and 2-week primaquine regimens, the rate of relapse in the first year after initial treatment is relatively high, whereas with 4-week and 8-week regimens, it was significantly reduced. An interesting finding was that no significant difference observed between 4- and 8-week regimens (p=0.57).

Different studies concerning the rate of relapse in vivax malaria patients during the first year, presented variable results. In a study in India, Gogtay *et al.*[6] reported 14% relapse in vivax malaria patients without antirelapse therapy. In another study they observed 11.7% relapse during the first six months[7]. In a similar study in Gujarat, it was 40% during the first eight months[8]. Other studies showed vivax malaria relapse is between 18 to 28%[9-12]. However, in a study in Thailand, a rate of 63% relapse by the end of two months after the initial treatment was reported[13].

In the present study, a considerable frequency of relapse (23.8%) by the end of first year occurred with 1-week antirelapse primaquine therapy. It seems that there is no difference between 1-week regimen and the absence of antirelapse therapy. However, it is mentioned that in Central America, administration of 45 mg primaquine along with chloroquine has considerably reduced the vivax malaria relapse[5]. Little is known about the effect of 2-week antirelapse regimen (3 tablets of 15 mg primaquine per week). A 5-day regimen using 15 mg per day is usually applied in India and Pakistan, which is comparable with 2-week regimen in terms of the drug total dose. It was found to reduce the relapse rate down to 2.6, 5.8 and 6.9%[8,9,14], which is lower than the relapse rate in our patients treated with 2-week regimen. However, in other studies in those countries, 26.7 and 51% relapse accompanied with 5-day therapy[7,15].

Four-week regimen of primaquine therapy has not been well discussed. The total dose of drug in this regimen is similar to that of 14-day period recommended by WHO for prevention of vivax malaria relapse. Relapse rate of 32, 0 and 17.5%, associated with 14-day regimen have been reported[7,15,16]. The relapse rate with 4-week regimen in our study was 5.4%, which is obviously lower than two mentioned studies. In most references, 8-week regimen is recommended to replace with 14-day regimen in the areas where the G6PD deficiency is highly endemic[17,18] although some references recommended a 6-week regimen[19]. The relapse rate is not clearly mentioned with the above regimens. The present study showed a rate of 4.6% with 8-week treatment regimen that is relatively low. Comparing of the NNT for the appearance of an additional relapse between 8-week and other regimens showed 5, 12 and 125 individuals with

1-week, 2-week and 4-week, respectively. This implies that the 2-week and in particular, 4-week regimens can be suitable replacements to the 8-week regimen in field situation.

No significant differences were observed between different genders or age groups, although Prasad[12] showed higher rates of relapse in patients aged 16 to 30 years and 3.5 times more among male.

It is noteworthy to mention that clinical surveys are not able to differentiate between relapse of vivax malaria and the reinfection with the parasite. This may confound the results in a vivax malaria endemic area. In our study this cannot interfere the results, as in Sistan and Baluchestan province the prevalence of vivax malaria during the time of study, was <15/1000 people and the estimated probability of reinfection was about 2/10,000 people that can be ignored.

The results showed that 4-week (intermittent) antirelapse primaquine therapies are not practically different from the 8-week regimen in preventing vivax malaria relapse. Furthermore, the value of NNH in this study showed that in the 4-week therapy, comparing to the 8-week regimen, only one more relapse per 125 patients is possible to happen. In other words, in 8-week treatment regimen comparing to the 4-week regimen, 500 additional trips to the patient's doors by health care workers are required, which is costly and time consuming. Considering the above, it is concluded that the 4-week treatment regimen can be used instead of 8-week regimen. Further research concerning the malaria relapse and possible connection with biological and genetic variability among different strains of *Plasmodium vivax* is required.

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