Original Article

Treatment of uncomplicated plasmodium falciparum malaria with quinine-doxycycline combination therapy

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Abstract

Objective: To assess the efficacy and tolerability of quinine-doxycycline combination therapy in uncomplicated falciparum malaria in terms of malarial parasite clearance from peripheral blood.

Methods: One hundred adult males were included in the study. Malarial parasite counts in peripheral blood films were determined at the time of admission and then 12 hourly until clearance and thereafter weekly for 28 days (4 weeks). Treatment was started with quinine sulphate 10mg of salt/kg body weight 8 hourly orally for a minimum period of 3 days and maximum of 7 days along with doxycycline 100 mg 12 hourly orally for 7 days. Primary efficacy outcome measure was early treatment failure, whereas secondary efficacy outcome measure was late treatment failure. Tolerability outcome measure was the development of treatment related adverse effects resulting in discontinuation from the study.

Results: The primary efficacy outcome measure of the study i.e. malarial parasite index declined from a mean of 6.34 (SD ± 2.83) before treatment to zero at day 7 of treatment. Parasite clearance time was 1-7 days (mean 3.58, SD ± 1.28). Mean duration of quinine treatment till clearance of malarial parasites was 4.63 days (SD +/- 1.38). Mean duration of fever was 2.96 days (range 1 to 6 days). There was no early or late treatment failure. There was no relapse during the 28 days follow up period. Drug related side effects were mild and did not warrant discontinuation of treatment in any patient.

Conclusion: Quinine-doxycycline combination is effective in southern Pakistan. Randomized controlled trials are needed to further validate the claim (JPMA 57:502:2007).

Introduction

Antimalarial drug resistance is now generally acknowledged to be one of the greatest threats to our ability to 'Roll back malaria'. The situation is worsening; with the rising incidence and increasing drug resistance.[1] Chloroquin resistant plasmodium falciparum malaria now predominates in Southeast Asia, South America and parts of Africa. Resistance to sulphadoxine-pyrimethamine is widespread in Asia and South America and is spreading in Africa and even quinine has become less effective over time.[1]

Situation is not different in Pakistan and falciparum malaria is on the rise.[2] Presently falciparum malaria accounts for 18% to 62% of all cases of malaria in different regions of Pakistan with resistance to one or more antimalarials reaching up to 40%.[3] Resistance of falciparum malaria to chloroquin is wide spread in Pakistan and it is no longer recommended.[4-6] Quinine is the drug of choice for P. falciparum but sporadic cases of resistant strains are being reported with monotherapy.[7,8] Artimisinin derivatives are presently effective but are costly for a developing country to be used on a mass scale.[9]

Recently use of antimalarials in combination with other antibiotics has been advocated in many countries.[3] The aims are twofold: to afford synergistic or additive killing of parasites, and to prevent emergence of drug resistance. Quinine has been used in combination with doxycycline, azithromycin and clindamycin.[10-12] All have been reported to be effective. There is paucity of reports in Pakistani medical literature describing the use of quinine based combination therapy. However it has been recommended in the guidelines of treatment of falciparum malaria.[3] We need to establish a baseline data regarding the efficacy and tolerability of quinine based combination therapy. Quinine with doxycycline is being used as first line therapy against falciparum malaria in our hospital because of easy access and low cost. We planned this study to assess the efficacy and tolerability of quinine in combination with doxycycline in Karachi.

Patients and Methods

A quasi-experimental study was carried out at the Department of Medicine, Combined Military Hospital Malir Cantonment Karachi Pakistan, from January 2003 to December 2004. Written informed consent was obtained from all patients. The medical ethics and scientific committee of the hospital approved the study.

The study population comprised of adult males presenting with high grade fever, positive thick and thin peripheral blood films for P. falciparum parasites and who had not taken any anti malarial treatment in the preceding 7 days. Whereas complicated malaria, mixed parasite infection, age less than 15 years, female patients, known hypersensitivity to any of the drugs used and persistent vomiting were excluded from the study.

After carefully fulfilling the inclusion and exclusion criteria, patients were admitted to the hospital to ensure compliance. A detailed history was recorded and physical examination performed. Blood samples were taken for routine haematology and biochemistry analysis which included complete blood count, platelet count, blood glucose fasting levels, serum urea and creatinine levels, urine for routine examination and microscopy, serum for liver function tests and disseminated intravascular coagulation screen. Parasite counts were determined at the time of admission and then 12 hourly in thin and thick films until clearance and thereafter weekly for 28 days. Parasite density was expressed as the number of parasites per microliter of blood, derived from the numbers of parasites per 1000 red blood cells in a thin film stained with Giemsa stain or was calculated from the white cell count and the numbers of parasites per 200 white blood cells in a thick film. Treatment was started with quinine bisulphate (tablet quinine bisulphate B.P. 300 mg, Lahore Chemical and Pharmaceutical Works, Lahore, Pakistan, batch no. 50271) 10mg of salt/kg body weight 8 hourly for a minimum duration of 3 days to a maximum duration of 7 days, till the clearance of malarial parasite from peripheral blood film, along with doxycycline (capsule vibramycin 100 mg, Parke Davis and Co. Ltd. Karachi, Pakistan, batch no. 658022) 100 mg 12 hourly for 7 days. Oral acetaminophen 1 gm 4 hourly was given for a temperature of > 38oC. Vital signs were recorded every 4 hours until resolution of fever and thereafter every 6 to 12 hours. Patients were examined twice daily for any adverse effects of the drugs or for the development of any complications of the disease. At the end of the treatment, patients entered observation period of 28 days during which peripheral blood films were checked weekly for malarial parasites and recurrence if any was noted. The patients were kept admitted to hospital for 28 days to better analyze late treatment failure as well as recurrence.

Malarial parasite index was calculated as WBC count/microlitre x parasite count/microlitre /100.[13] Primary efficacy outcome measure was early treatment failure defined as a parasite count on day 2 > or equal to 75% of that on day 0. Secondary efficacy outcome measure was late treatment failure defined as persistence of malarial parasites in the peripheral blood film beyond 14 days as per WHO protocol.[14] Tolerability outcome measure was the development of treatment related adverse effects resulting in discontinuation from the study.

All the statistical analyses were done using statistical program SPSS ver. 12.0. The mean with standard deviation, frequency and percentages were reported. Significance was tested at $p<0.05$ and confidence interval at 95%. Continuous data were compared using paired sample t-test.

Results

Hundred patients entered the study and all completed it. Patient profile and variable characteristics are given in Table 1. Mean age was 31 years ± 9.43 (Range 16 to 49 years) and mean duration of fever was 2.96 ± 1.3 days (range 1 to 6 days). Fever lasted for 3 days in maximum number of patients (32) and for 6 days in only 5 patients. Mean duration of quinine treatment till clearance of malarial parasites was 4.63 ± 1.38 days (range 1 to 7 days). Duration of treatment was 5 days in maximum number of patients (33) while only 6 patients had to take quinine for 7 days.

The primary efficacy outcome measure of the study i.e. malarial parasite index declined from a pretreatment range of 0.10 to 13.80 (mean 6.34, SD ± 2.83) to zero at day 7 of treatment. Details of malarial parasite index are given in Table 2. Mean parasite clearance time was 3 days (range 1 to 7 days). No early and late treatment

Table 1. Patient profile.

Total patients (All males)	100
Mean age (range)	31(16-49) years SD 9.433
Mean axillary temperature (range)	37.2 (35.2-39.4)*C
Parasite clearance time in days (range)	3.58 (1-7)
Fever clearance time in days (range)	2.96 ± 1.3 (1-6)
Duration of treatment in days (range)	4.63 ± 1.37 (3-7)
Early treatment failure	Nil
Late treatment failure	Nil
Drop outs	Nil
Complications of therapy	Nil

Table 2. Mean values of primary end point i.e. malarial parasite index.

	N	Minimum	Maximum	Mean	SD	p
MPI-day 1	100	.10	13.80	6.3440	2.8357	
MPI-day 2	100	.00	10.60	2.9950	1.9848	0.0001
MPI-day 3	91	.00	8.50	1.3681	1.3315	0.0001
MPI-day 4	81	.00	5.60	.5284	.7762	0.0001
MPI-day 5	60	.00	3.50	.2000	.5029	0.0001
MPI-day 6	27	.00	.60	5.185E-02	.1312	0.0001
MPI-day 7	6	.00	.00	.0000	.0000	0.0000

MPI=malarial parasite index, p value significant at 0.05, calculated by paired sample t test, using pairs of MPI 1 with MPI 2 up to MPI 7, SD=standard deviation.

failures were seen among the patients. Tolerability outcome measure was also not met as all patients completed the treatment. During the 28 days observation period there was no recurrence and all patients were discharged from the hospital in good health.

Discussion

Estimates of burden of malaria in terms of drug resistance suggest that demise of chloroquin is the single most plausible factor contributing to malaria related mortality which has at least doubled in the last 15 years.[15] Because it is difficult to control drug resistance once it has emerged, there is a need for strategies that prevent the rare event of initial emergence. Combinations of drugs which have different molecular targets delay the emergence of resistance. However, malaria control programs may be reluctant to adopt this strategy because until resistance emerges there is no evident benefit to the more expensive combination treatment.[1]

Tetracyclines were found to have antimalarial activity about 35 years ago.16 Tetracycline depresses the activity of dihydroorotate dehydrogenase of the pyrimidine pathway in P. falciparum. Recently invitro activity of doxycycline on 71 P. falciparum isolates has been determined and compared with chloroquin, quinine, amodiaquin, artemether, pyrimethamine and cycloguanil. Doxycycline was found to be equally effective against chloroquin resistant and chloroquin sensitive isolates. In addition, doxycycline did not show cross resistance with any of the drugs tested. Authors conclude that doxycycline and amino-4-quinolines have different sites of action which makes these drugs a favourable combination to suppress drug resistance.[16]

This study has shown a mean parasite clearance time of 3 days which is consistent with other studies from around the world. Alecrim et al compared quinine-doxycycline combination with artemether-lumefantrine and reported a parasite clearance time of 3 days for quinine-doxycycline combination.[17] Miller et al used quinine-doxycycline combination in 60 volunteers in Thailand and achieved 100% cure rates in 7 days.[12]

In this study side effect profile of treatment was tolerable and in no patient did it warrant stopping therapy. This finding of low drug related complications is consistent with other reports from our local literature.[18] Khan et al compared the side effect profile of quinine and artemether in a comparative trial and found negligible side effects of quinine.[19] Haider et al compared quinine with artemether and found few side effects in quinine group which did not affect treatment.[20] On the other hand Khan et el,[3] have stated a high complication rate with moderate efficacy of quinine-doxycycline combination which is contrary to our findings. Results consistent with our findings in regard to efficacy and tolerability have been found by other authors around the world.[12,16,21-23]

Compliance has been stated as a problem with quinine combination therapies. To overcome this problem and to ensure reliable efficacy assessment we kept the patients admitted to our medical unit for the complete duration of study. However, this is not a practical solution. It might help in the drug efficacy assessment but when applied to the patients' environment, compliance problems have to be kept in mind. Patient education can help overcome this problem.

Cost of treatment is an important factor in determining the best possible antimalarial therapy in a developing country. Although artemisinin based combination therapy has been advocated to replace falciparum malaria treatment in many parts of the world but the cost is about 10 times more than quinine based combination therapy.[1,3,9] This can lead to another set back in the battle against malaria. Health services in Pakistan will be unable to absorb the impact with the present resources. Based on the findings of this study, we therefore recommend that quinine based combination therapy should be the first line therapy against falciparum malaria and other treatments should be reserved for selected cases.

The present study has its limitations. It was a quasi-experimental open clinical trial with the study population not being a true representative of local population as it comprised of soldiers coming from different areas of Pakistan. Complicated and severe malaria as well as female patients were excluded. Extensive data collection from different endemic areas of Pakistan is necessary to detect early drug resistance to malaria. Moreover, a baseline data will also be provided for comparison with future studies. Randomized, controlled trials will be helpful in validating the findings.

Conclusion

This study concludes that quinine-doxycycline combination is effective in southern Pakistan. It is hoped that this will encourage further research in finding other effective combination drugs to be used with quinine to enhance its efficacy and delay development of resistance against falciparum malaria.

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