Study of the effect of single does primaquine on gametocytaemia and infectivity among Amodiaquine–treated *P. falciparum* malaria patients

Tin Shwe[**], *Khine Khine Win*[*] & *Pe Than Myint*[**]

* M. Sc student (Zoology)

** Clinical Research Unit (Cerebral & Complicated malaria) Department of Medical Research

One hundred and five patients who attended Thayarwady Civil Hospital during 1987 and 1988 malaria seasons were studied. They were divided into three groups. Among 35 patients who were treated with amodiaquine alone, 23-33% of the patients showed gametocytes in blood during days 14, 21 and 28 of therapy. Among those patients with gametocytes in blood, 50 to 63% of patients showed that they were viable by exflagellation method. Follow-up of one patient showed viable gametocytes in blood till 51st day of drug therapy. Among 45 patients treated with amodiaquine and primaquine (45mg single dose given on day 3), 31% of patients showed gametocytes on day 7, later only 0-10% of patients showed gametocytes on day between 14, 21 and 28. Among the patients with gametocytes in blood 25% of the patients showed that they were viable till day 4. From day 5 they were not viable. Except one patient who showed gametocytes at day 28 was proved to be RII resistant to amodiaquine. Among 25 patients treated with amodiaquine and primaquine (45 mg single dose : given on day 1 of hospital admission) 36% showed gametocytes on day 7 and 42% showed gametocytes on day 28. Of these 26% patients with gametocytes which appeared on day 28 was proved to be viable. It is suggested that primaquine 45mg is effective to control infectivity of gametocytes in blood. It is also suggested that primaquine should be given on 3rd day of hosptital admission to get the most beneficial effect.

INTRODUCTION

To have a significant impact on the transmission of falciparum malaria, Pan American Health Organization in 1982 (1) made the recommendation that Primaquine should always be administered whenever a schizontocidal drug is used.

As a part of an effort to interrupt transmission of drug resistant strain, World Health Organization Scientific Group meeting in 1984 (2) also suggested that a single dose of 45mg primaquine base be given to sterilize the gametocytes. They also noted that research is needed to determine the optimum schedule for such a combination.

In the months and years that have passed since these meeting, there has been little effort to follow these recommendations. A search of the files of the National Medical Library for 1984 and 1985 produced 58 references to primaquine and not one relates to these recommendation (3). Some studies on primaquine was undertaken in Thailand.

Chomcharn et al (4) conducted the study of the effect of single dose primaquine on

P. falciparum gametocytaemia and mosquito infectivity in Thailand. They found that 10 patients with gametocytaemia when given 45mg primaquine were all cleared by day 6, but among the controls gametocytes were positive up to day 17.

Bunnag et al (5) had also conducted field trial of 3 regimens of primaquine (15mg daily X 5 days, 30 mg single dose and 45 mg single dose) on 121 patients with initial gametocytaemia. They reported that the gametocytes disappeared by day 21 in all groups. In the 194 patients without initial gametocytaemia, gametocytes developed in over 25% of them. They cleared again on day 28.

They commented that further work on the infectivity of the gametocytes is required.

But in our experience, with 45mg primaquine given on day 1 of hospital admision to falciparum malaria patients together with 1500mg amodiaquine or 1500mg sulphadoxine and 75mg pyrimethamine gametocytes persisted in blood of 7 out of 23 patients at day 7 and on 1 out of 5 patients at day 28. Thus there may be persistance of gametocytes in Myanmar patients though they were treated with 45mg primaquine. Thus this study is needed.

PATIENTS AND METHODS

One hundred and five patients who attended Thayarwady Civil Hospital during 1987 & 1988 malaria seasons were studied. Thirty five patients with falciparum malaria parasite in blood with parasite counts 1000-200,000/cumm were treated with amodiaquine (total dose of 1500 mg divided in 3 days). The presence and viability of gametocytes in blood were followed at day 1,3,7,14,21 and 28. One patient who had gametocytes in blood throughout this study was followed weekly till his gametocytes were disappeared from circulation.

Second group of 45 patients with P. falciparum malaria were treated with amodiaquine (dose as above)and primaquine 45mg single dose- the later was given on 3rd day of hospital admission. The presence of gametocytes and viability were followed on days mentioned above.

Third group of 25 patients with P. falciparum in blood were treated with amodiaquine (dose as above) and primaquine 45mg single dose given at day 1 of hospital admission. They were also followed as above.

Viability of gametocytes were tested by incubation of blood on glass slide with a drop of normal saline and storing in -20° C for 5-10 minutes. The presence of exflagellation of male microgametocyte was recorded as an indicator of viability.

RESULTS

Among the 35 patients treated with amodiaquine alone, 23-33% of the patients showed gametocytes in blood during days 14, 21 and 28 of therapy. Among those patients with gametocytes in blood, 50-63% of patients showed that they were viable by exflagellation method. Follow-up of one patient showed viable gametocytes in blood till 51st day of drug therapy.

Among 45 patients treated with amodiaquine and primaquine (45mg single dose : given on day 3), 31% of patients showed gametocytes on day 7, later only 0-10% of the patients showed gametocytes on days between 14 and 28. Among the patients with gametocytes in blood 25% of the patients showed that they were viable till day4. From day 5 onwards they were not viable. At day 28, gametocytes reappeared in 1 patient. He was proved to be viable. He was also resistant at RII level to amodiaquine.

Among 25 patients treated with amodiaquine and primaquine (45mg single dose; given on day 1 of hospital admission) 36% showed gametocytes on day 7 and 42% showed gametocytes on day 28. Of these patients with gametocytes which appeared

Table: Percentage of patients with Gametocytes and their viability among patients treated with three groups of drugs

Days	AMQ (1.5G) only N = 35		AMQ (1.5G) with Primaquine 45 mg on Day 3 N = 45		AMQ (1.5G) with Primaquine 45 mg on Day 1 N = 25	
	% of patients with gametocytes	% with viable gametocytes	% of patients with gametocytes	% with viable gametocytes	% of patients with gametocytes	% with viable gametocytes
1	60	90	53	78	50	40%
3	54	90	43	25*	40	0%
7	56	70	31	0	36	10%
14	33	63	7	0	-**	-**
21	23	50	0	0	-**	-**
28	30	50	10	-	42	28%

* Done on Day 4.
** Not Done.

on day 28, 28% was proved to be viable. See Table 1 for details.

DISCUSSION

Mackerras and Ercole (7), Jeffrey et al (8) and Rieckmann et al(9), had reported the action of primaquine on gametocytes as quick action (in 6-12 hours infectivity is lost) and P. falciparum gametocytes are effectively eliminated from the circulation in 2 to 4 days.

Rieckmann et al (9), Burgess and Bray (10) and Chomcharm et al (4) had all reported disappearance of gametocytes when treated with 45mg primaquine by day 6 (4-8 days).

Bunnag et al (5) from their studies in Thailand also reported persistence of gametocytes after various dose of primaquine till day 21. In this study there were persistence of gametocytes after primaquine even at day 28. This delay in the disappearance of gametocytes in the circulation after primaquine in patients from Myanmar and Thailand could be due to development of partial resistance of gametocytes to eliminate from circulation after primaquine.

But as all the gametocytes that are persisting in circulation are not viable (except one patient with RII resistance to amodiaquine) we can assume that this present treatment regimen. Primaquine given on day 3 of patients admission is effective to control viable gametocytes in blood.

Among the patients treated with amodiaquine primaquine given on 1st day of hospital admission, 36-42% of patients had reappearance of gametocytes in blood betwen days 7 and 28. Of these two patients who had reappearance of gametocytes at day 28 was tested for viability. One of them was proved to be viable.

Since the half life of primaquine is very short probably the single dose of primaquine may have the ability to clear the gametocytes already in the circulation but it may have no ability to remove new gametocytes which are released into circulation from the still living trophozoites of RII level resistant patients.

Similar reasons may be given for patients who were treated with primaquine at day 1 instead of day 3.

Thus untimely administration of the drug (primaquine given on day 1 instead of day 3) may be the cause of failure of the action of primaquine. From this study, we support the idea of adding primaquine to schizontocidal drugs but we suggest to give primaquine on day 3 of treatment, when the malaria parasites almost disappeared from circulation instead of day 1.

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