MALARIA PROPHYLAXIS WITH DOXYCYCLINE IN SOLDIERS DEPLOYED TO THE THAI-KAMPUCHEAN BORDER

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INTRODUCTION

Multi-drug-resistant falciparum malaria is the greatest medical threat to Thai soldiers deployed along the Thai-Kampuchean border. A longitudinal study of Royal Thai Marines showed annual malaria attack rates approaching 1,000/1,000 men. (AFRIMS' report to Royal Thai Navy Surgeon General 11 May 88). This was despite routine prophylaxis with pyrimethamine/dapsone (Maloprim, Wellcome). Prophylaxis with chloroquine and pyrimethamine/sulfadoxine (Fansidar, Hoffman La Roche) has been shown to be only about 50% effective in a study of Royal Thai Army troops. (Singharaj *et al.*, 1987).

The use of quinine and tetracycline to treat cases of drug-resistant falciparum malaria suggested that tetracylines might be effectively used in chemoprophylaxis. (Reacher *et al.*, 1981) Daily doxycycline (100 mg/day) was found to be an effective prophylactic in Karen school children on the Thai-Burmese border. (Pang *et al.*, 1987) Further closely controlled studies in Royal Thai Army soldiers demonstrated doxycycline's effectiveness on the Thai-Kampuchean border. (Singharaj *et al.*, 1987) The current study was designed to determine whether doxycycline could be used effectively by military units under actual conditions of field operations on the Thai-Kampuchean border. If doxycycline could be effective without extra medical personnel to ensure compliance, then a much wider use of doxycycline to control malaria in Thai troops could be actively considered.

METHODS

This was a unblinded drug trial done in units of the Fourth Controlling Headquarters of the Royal Thai Marine Tahaan Pran. These units of paramilitary militia are regionally organized for border defense and other missions. This particular unit was deployed in Chantaburi province along the Thai-Kampuchean border in an area of high malaria endemicity. The study was conduct-

ed from November 1987 to February 1988.

A total of 609 men participated in the study. Participation was defined as taking medication for at least 14 days and having at least three malaria smears over the course of the 119 day study. Malaria smears were made every 10 days by the unit medics and sent to the headquarter area where they were read by the Royal Thai Navy (RTN) Preventive Medicine team and confirmed by AFRIMS' technicians. A malaria case was a soldier who demonstrated malaria parasitemia following two previously negative smears. A negative smear was defined as no parasites seen after the examination of 200 oil immersion fields of a Giemsa-stained thick smear preparation by experienced medical technicians.

Three drug groups were randomly assigned, in a ratio of 2:2:1, to receive either 50 mg doxycycline daily, 100 mg doxycycline daily, or weekly pyrimethamine 12.5 mg + dapsone 100 mg, the standard drug used by other RTN units. Medication was provided by AFRIMS and was administered by unit medical personnel. Compliance was not enforced by the investigators. The doxycycline used was Vibramycin supplied by Pfizer International Corp. Pyrimethamine/dapsone (Maloprim) was obtained from Wellcome Foundation Ltd. The soldiers were regularly questioned about any side-effects related to these drugs.

RESULTS

A summary of the malaria attack rates seen in each drug group is shown in Table 1. A total of 189 separate malaria infections were seen in 609 men in the eight companies studies. Since this study was conducted without a placebo group, it is difficult to calculate a precise figure for the efficacy of these drugs. However, since the standard of care in this population is the weekly use of Maloprim, this can be taken as the base-line efficacy of 1.0 and the relative efficacy of the other drugs can be calculated accordingly. The 100 mg regimen of doxycycline was 64% better than Maloprim in preventing malaria ($P < .0001$) while the 50 mg regimen was 38% better. In addition, the 100 mg regimen was 42% better than the lower dose in preventing malaria. More importantly, it was 53% better in preventing falciparum malaria while the 50 mg regimen was not statistically better than Maloprim in preventing vivax malaria ($X^2 = 1.26$; $P = .18$). These figures compare favorably with the results of two previous studies in which the compliance with doxycycline was strictly enforced. (Singharaj *et al.*, 1987; Pang *et al.*, 1987)

Overall compliance with these regimens was relatively high: 73% for the doxycycline groups and 79% for the Maloprim group. Compliance by company is shown in Table 2. In the doxycycline drug groups, more than 50% of the men took daily medication at least 75% of the time and over 95% took daily medication more than half of the time. As a weekly drug, Maloprim is easier to administer. It showed 70% compliance at least 75% of the time and 99% of the men took more than half of the scheduled medication. The data were also analyzed to determine if there was evidence that the men tired of the daily medication. We looked at the number of days of missed medication for the three drug regimens during the first, middle and final thirds of the study. Absenteeism increased from 5% to 15% over the course of the study but, there were no differences between those taking daily versus weekly medication.

More than 90% of the expected smears

Table 1

Results of a trial of doxycycline as a malaria prophylactic in RTN troops on the Thai–Kampuchean border

Medication	Men	PF	PV	All malaria	Infections/ 100 men	Relative efficacy
Doxy 100	243	18	28	46	19	1.6
Doxy 50	243	38	41	79	32	1.4
Maloprim	123	25	39	64	52	1.0

* the study lasted 17 weeks from 1 Nov. 87 to 27 Feb. 88

Table 2

Participation and Compliance by Company

Company	Men in study		% meds taken		% smears completed
	Malo	Doxy*	Malo	Doxy*	
A	20	75	86	69	97
B	15	60	87	85	89
C	14	59	74	70	92
D	16	59	76	72	90
E	12	59	77	66	95
F	17	63	84	78	91
G	15	56	72	70	91
H	14	55	69	72	90
overall	609		79%	73%	92%

* the two doxycycline groups are combined here

were collected (Table 2). Participation was uniform for all eight companies as measured by days on medication and by number of smears made.

No serious medication side-effects were seen. Minor problems were reported so rarely that effective analysis could not be done.

DISCUSSION

The choice of chemoprophylactic agents against malaria for soldiers on the Thai–Kampuchean border is complex. Few drugs are effective against drug-resistant *Plasmodium falciparum*. Compliance with medications is often poor when multiple doses are required. Significant side-effects or

cost factors can also limit a drug's practical usefulness under operational conditions. In the light of these problems, doxycycline has performed well. When taken on a 100 mg daily dose schedule, it was approximately 80% effective in preventing malaria in an area of falciparum malaria with previously known resistance to chloroquine and pyrimethamine/sulfadoxine. These results confirm the studies of 50 and 100 mg doses in Karen school children. (Pang *et al.*, 1988)

This study has shown that under operational conditions, compliance with daily drugs in this group of men was nearly as good as that for the weekly drug regimen and that few side-effects were reported. Even when not every soldier took doxycycline every day, those taking doxycycline were protected from malaria better than the group taking pyrimethamine/dapsone. This greater efficacy would reduce the number of malaria cases in the Thai military to less than half its present level.

Doxycycline does not represent a perfect prophylactic drug. There is a high incidence of vivax malaria relapses if it is stopped abruptly and it is relatively expensive. However, given the current situation of the Thai Armed Forces on the Thai–Kampuchean border, doxycycline represents an option which is more efficacious than currently used chemoprophylactic regimens.

SUMMARY

A battalion of Royal Thai Marine militia was assigned to take either 50 mg or 100 mg of doxycycline daily or pyrimethamine/dapsone weekly for malaria prophylaxis on the Thai–Kampuchean border for a 17 week period. Attack rates for the groups expressed as cases/100 men were 34 for 50 mg doxycycline, 18 for 100 mg doxycycline, and 52 for pyrimethamine/dapsone. The relative efficacy of the two doxycycline regimens compared to Maloprim were 1.6 and 1.4. Compliance with the daily drug nearly equalled that of the weekly regimen. This suggests that 100 mg of doxycycline daily can be effectively used for malaria prophylaxis by soldiers under operational conditions on the Thai–Kampuchean border.

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