

SHORT REPORT: A CONSIDERATION OF PRIMAQUINE DOSE ADJUSTMENT FOR RADICAL CURE OF *PLASMODIUM VIVAX* MALARIA

ELI SCHWARTZ, GILI REGEV-YOCHAY, AND DANIEL KURNIK

Center for Geographical Medicine and Department of Medicine C, Infectious Disease Unit, and Department of Medicine A, Chaim Sheba Medical Center, Tel Hashomer, Israel

Abstract. Relapse of *Plasmodium vivax* malaria following standard primaquine dosing has been reported from many areas, and more recently from sub-Saharan Africa. In this report we describe eight episodes (in five patients) of treatment failure in non-immune Israeli travelers returning from Ethiopia. Retrospective calculation of the primaquine dose per kilogram of body weight for 23 treatment courses showed a lower total dose per kilogram in heavier patients. The mean calculated dose (95% CI) in the eight failed treatments was 2.5 ± 0.3 mg/kg compared with 4.4 ± 0.5 mg/kg in the 15 successful treatment courses. Weight-adjusted dosing regimens may prevent inadvertent sub-therapeutic drug failure, and thus apparent primaquine failure. In these cases, no relapses were observed in those who received > 3.5 mg/kg. Consideration should be given to adjusting the dose of primaquine according to body weight. For those infected by strains from Ethiopia a dose > 3.5 mg/kg is preferable.

Although *Plasmodium vivax* accounts for less than 10% of the malaria cases in Africa, there has been an increase in recent accounts of infection among travelers to these regions, such as Israelis returning from Ethiopia¹ and U.S. military returning from Somalia.² Reports of primaquine failures have also increased, primarily from Papua New Guinea, Southeast Asia, and Central and South America.^{3–7} Relapses following primaquine treatment of strains acquired in Africa have been less well described.

We report eight relapses (in five individuals) of *P. vivax* malaria in Israeli travelers to Ethiopia despite a standard dose of primaquine. The dose per kilogram of body weight was calculated for each treatment course and the doses resulting in successful treatments were compared with those resulting in relapses.

This study consisted of a retrospective review of the authors' patient records; the patients had been treated according to accepted clinical guidelines. Therefore, when the matter was referred to the Helsinki Committee of Sheba Medical Center, it was determined that no other ethical review process was necessary.

Charts of 15 Israeli travelers who presented at the Sheba Medical Center with smear-documented *P. vivax* malaria between January 1995 and June 1998 were reviewed. All had returned from Ethiopia; all had presented at least three months following return, and 12 of 15 had been on rafting tours of the Omo River. They had received mefloquine or doxycycline chemoprophylaxis, and had reported good compliance. None was given primaquine for terminal prophylaxis. Primary attacks were treated with chloroquine followed by 15 mg/day of primaquine (Sanofi-Winthrop, New York, NY) for 14 days. Compliance was assessed by interviews at the completion of the treatment course. None had traveled again to malarious areas.

Five of the 15 malaria patients had relapses between 3 and 10 months after initial treatment, and were treated with chloroquine followed by greater doses or longer courses of primaquine (Table 1). After an additional 3–10 months, three of five patients experienced a third episode of malaria, and were given a third course of a higher dose primaquine (Table 1). There were no further relapses, and the remaining 10 patients remained disease-free on follow-up at 12–36 months.

The five patients that had at least one relapse had initially received lower mean doses of primaquine based on body weight than the 10 patients who did not have a relapse (95% CI; 2.4 ± 0.4 versus 4.0 ± 0.5 ; $P = 0.018$, Fisher's exact test). Comparison of the primaquine doses by weight between the eight courses (in five patients) resulting in relapse and the 15 successful courses showed no relapses when doses > 3.5 mg/kg of primaquine were used (Figure 1). No adverse events were observed and methemoglobin levels, which were measured in patients who were treated with the higher doses, were in the normal range.

The dosage recommendation for radical cure of *P. vivax* malaria is based on several studies performed during the 1950s.^{8,9} Since then, reports of primaquine resistance or primaquine failure have become fairly common from areas such as Papua New Guinea, Southeast Asia, India, and Colombia.^{3–7,10–12}

These five cases originating in Ethiopia support other reports suggesting that the incidence of *P. vivax* malaria in east Africa, and its failure to respond to standard doses of primaquine in this area, may actually be higher than suspected.^{1,2}

Relapses despite primaquine treatment may reflect changes in primaquine response among formerly susceptible strains, or geographic spread of strains that have long been known to be refractory. However, the term resistance may be misleading. The presence of drug resistance involving antimalarials is generally assessed by the effect a drug has on the asexual parasite density in the blood, or on the time to parasite recrudescence in the presence of adequate anti-malarial drug levels in the serum. Because primaquine has little effect on erythrocytic parasites, asexual parasite density cannot be used to demonstrate drug resistance, and thus it is difficult to define true resistance. Controversy exists as to whether drug resistance is indeed the cause for cases of primaquine failure. It has been suggested that resistance to primaquine may actually reflect unrecognized chloroquine resistance with incomplete eradication of the erythrocytic stage rather than the hepatic forms. However, early relapses within one month of appropriate chloroquine and primaquine treatment are characteristic of chloroquine failure, while late relapses usually represent primaquine failure.¹³

Geographic diversity and susceptibility to primaquine ex-

TABLE 1
Summary of the 5 patients who failed primaquine treatment

Case no.	Weight (kg)	Prophylaxis	First primaquine treatment		Second primaquine treatment		Third primaquine Rx		Outcome—free of attack	
			Treatment course	Total dose	Interval to first relapse	Treatment course	Total dose	Interval to second relapse		Treatment course
1	97	Mefloquine	15 mg for 14 days	2.2 mg/kg	3 months	15 mg for 14 days	2.2 mg/kg	30 mg for 20 days	6.2 mg/kg	30 months
2	100	Mefloquine	15 mg for 14 days	2.1 mg/kg	3 months	15 mg for 21 days	3.15 mg/kg	30 mg for 20 days	6.0 mg/kg	36 months
3	85	Mefloquine	15 mg for 14 days	2.5 mg/kg	10 months	15 mg for 14 days	2.5 mg/kg	30 mg for 14 days	4.9 mg/kg	12 months
4	95	Doxycycline	15 mg for 14 days	2.2 mg/kg	5 months	15 mg for 14 days + 30 mg for 7 days	4.4 mg/kg	NA	NA	14 months
5	66	Doxycycline	15 mg for 14 days	3.2 mg/kg	6 months	15 mg for 21 days	4.8 mg/kg	NA	NA	18 months

NA = No second relapse, no further treatment.

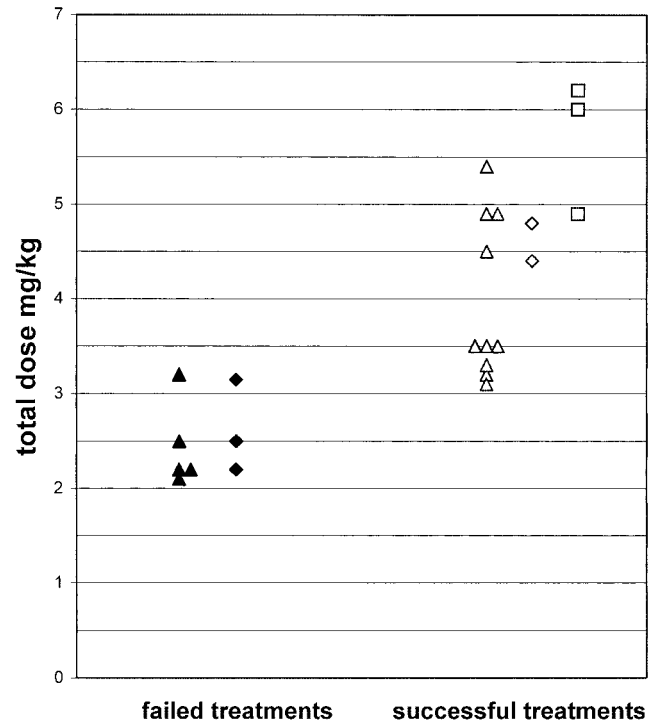


FIGURE 1. Failed treatments for *Plasmodium vivax* malaria compared with successful treatments. Δ = first malaria attack, successful treatment; \blacktriangle = first malaria attack, failed treatment; \diamond = second malaria attack, successful treatment; \blacklozenge = second malaria attack, failed treatment; \square = third malaria attack, successful treatment.

ist among *P. vivax* strains, although patients infected with the same strain can show different responses to primaquine based on individual pharmacokinetic variations.¹⁴ In addition, the standard fixed dose of primaquine results in doses per kilogram of body weight that are quite variable. For example, a 14-day course of treatment translates into 3.5 mg/kg for a 60-kg patient and 2.3 mg/kg for a 90-kg patient. Thus, inadvertent subtherapeutic dosing may be a cause for primaquine failure in heavy patients. In the Israeli patients, dose-adjustment for body weight resulted in a radical cure for all patients after receiving at least 3.5 mg/kg. Dose adjustment by weight also allows a direct comparison of the adequacy of primaquine in treating infections with *P. vivax* strains worldwide. In Southeast Asia and Papua New Guinea, doses of approximately 6 mg/kg are required for effective cure of relapse, whereas none of the patients harboring strains from Ethiopia relapsed after doses > 3.5 mg/kg.

Although an interesting observation, there may be other explanations for such findings: 1) poor compliance; 2) repeated treatments, even with standard dosing, could have resulted in cures; and 3) although patients were followed for more than 12 months, some could relapse thereafter.

Careful observation by clinicians treating patients with *P. vivax* malaria will help clarify this problem, but in the interim, consideration should be given to determining the dose of primaquine for radical cure by body weight.

Acknowledgment: We thank Dr. Phyllis Kozarsky for her critical review of the manuscript.

Authors' addresses: Eli Schwartz, Center for Geographical Medicine

and Department of Medicine C, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel. Gili Regev-Yochay, Center for Geographical Medicine and Infectious Disease Unit, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel. Daniel Kurnik, Center for Geographical Medicine and Department of Medicine A, Chaim Sheba Medical Center, Tel Hashomer 52621, Israel.

REFERENCES

1. Schwartz E, Sidi Y, 1998. New aspects of malaria imported from Ethiopia. *Clin Infect Dis* 26: 1089–1091.
2. Smoak BL, DeFraités RF, Magill AJ, Kain KC, Wellde BT, 1997. *Plasmodium vivax* infections in U.S. army troops: failure of primaquine to prevent relapse in studies from Somalia. *Am J Trop Med Hyg* 56: 231–234.
3. Looareesuwan S, Buchachart K, Wilairatana P, Chalermrut K, Rattanapong Y, Amradee S, Siripiphat S, Chullawichit S, Thiamasan K, Ittiverakul M, Triampon A, Walsh DS, 1997. Primaquine-tolerant vivax malaria in Thailand. *Ann Trop Med Parasitol* 91: 939–943.
4. Nayar JK, Baker RH, Knight JW, Sullivan JS, Morris CL, Richardson BB, Galland GG, Collins WE, 1997. Studies on primaquine-tolerant strain of *Plasmodium vivax* from Brazil in *Aotus* and *Saimiri* monkeys. *J Parasitol* 83: 739–745.
5. Arias AE, Corredor A, 1989. Low response of Colombian strains of *Plasmodium vivax* to classical antimalarial therapy. *Trop Med Parasitol* 40: 21–23.
6. Gascon J, Gomez-Arce JE, Menendez C, Valla ME, Corachan M, 1994. Poor response to primaquine in two cases of *Plasmodium vivax* malaria from Guatemala. *Trop Geogr Med* 46: 32–33.
7. Jelinek T, Nothdurft HD, Von Sonnenburg F, Loscher T, 1995. Long-term efficacy of primaquine in the treatment of vivax malaria in nonimmune travelers. *Am J Trop Med Hyg* 52: 322–324.
8. Garrison PL, Hankey DD, Walter GC, Donovan WN, Jastremski B, Alving AS, 1952. Cure of Korean vivax malaria with pamaquine and primaquine. *JAMA* 149: 1562–1563.
9. Cooper WC, Myatt AV, Hernandez T, Jeffrey GM, Coatney GR, 1953. Studies on human malaria. XXXI. Comparison of primaquine, isopentaquine, SN-3883, and pamaquine as curative agents against Chesson strain vivax malaria. *Am J Trop Med Hyg* 2: 949–957.
10. Clyde DF, McCarthy VC, 1977. Radical cure of Chesson strain vivax malaria in man. *Am J Trop Med Hyg* 26: 562–563.
11. Martelo OJ, Smoller M, Saladin T, 1969. Malaria in American soldiers. *Arch Intern Med* 123: 383–387.
12. Fisher GU, Gordon MP, Lobel HO, Runcik K, 1970. Malaria in soldiers returning from Vietnam: epidemiologic, therapeutic, and clinical studies. *Am J Trop Med Hyg* 19: 27–39.
13. Collins WE, Jeffery GM, 1996. Primaquine resistance in *Plasmodium vivax*. *Am J Trop Med Hyg* 55: 243–249.
14. Ward SA, Mihaly GW, Edwards G, Looareesuwan S, Phillips RE, Chanthavanich P, Warrell DA, Orme ML, Breckenridge AM, 1985. Pharmacokinetics of primaquine in man. II. Comparison of acute versus chronic dosage in Thai subjects. *Br J Clin Pharmacol* 19: 751–755.