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Primaquine Dosing Errors: The Human Cost of a Pharmaceutical Anachronism

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Abstract. Confusion between salt/base forms of primaquine may result in malaria prophylaxis failure. During 1995–2011, there were 14 malaria cases in Israel despite primaquine primary prophylaxis. In 6/14 cases, primaquine was underdosed because of confusion between salt and base forms, including two *Plasmodium falciparum* cases. Primaquine labeling clarification may be lifesaving.

INTRODUCTION

Primaquine was introduced as an antimalarial drug during the early 1950s.[1]

It remains a cornerstone of the treatment of *Plasmodium vivax* and *P. ovale*, and as a gametocydal agent for *P. falciparum*.[2] In recent years, its indications have been expanded to include malaria prophylaxis, both primary and terminal, especially in areas where *P. vivax* is highly endemic.[3]

The efficacy of primaquine is dose dependent, and the recommended daily dose is 30 mg primaquine base. Primaquine tablets are usually composed of 26.3 mg primaquine phosphate salt, which is equivalent to 15 mg primaquine base.

Primaquine is one of a few drugs where pill strength is expressed on labeling as both salt and base forms. The dual description of drugs in both their salt and base form is a pharmaceutical anachronism, which is no longer endorsed by the U.S. Pharmacopeial Convention (USP),[4] as it may contribute to prescription errors. However, the role such errors may play in malaria prophylaxis failure is not reported in the medical literature.

The aim of this study was to show the role of prescription errors relating to salt/base labeling of primaquine, in prophylactic failure and malaria attacks.

METHODS

This study was a retrospective case series.

In Israel, malaria is a notified disease, and all cases are reported to the Ministry of Health. Each case of malaria is evaluated by trained epidemiological staff close to the event by interview and by review of hospital data. Reports contain epidemiological data (including travel history, use of chemoprophylaxis), clinical data (including treatment outcome), and microbiological data (including confirmation of *Plasmodium* species).

We evaluated all cases of malaria reported in the national malaria registry from the period of 1995–2011. All cases involving the use of primaquine prophylaxis were included. Demographic, epidemiologic, and clinical data were extracted.

Case definition: all cases of malaria that occurred despite primary prophylaxis with primaquine. The cases were further divided according to the actual primaquine dosing, either 30 or 15 mg base/day.

The study was approved by the Institutional Review Board of the Sheba Medical Center.

RESULTS

During the study period, 690 cases of malaria had occurred in returning Israeli travelers, of whom 14 patients developed in total 16 attacks of malaria despite the use of primary primaquine prophylaxis. All 14 cases involved travelers returning from rafting trips to the Omo River in Ethiopia. All travelers were healthy young adults, were not taking any other medications, and none had traveled again to malarious areas between the index trip and the malaria attack. Clinical details of these patients are presented in Table 1.

In 6/14 (42.8%) patients, malaria developed after primaquine dosing errors had occurred, and patients had been issued or took a single daily tablet (half the recommended dose—each tablet contains 26.3 mg of primaquine [equivalent to 15 mg of primaquine base]) under the assumption that this approximated the recommended 30 mg dose.

In two of these cases, *P. falciparum* attacks occurred within 1 month after return and were followed by a late *P. vivax* attack as well. The other four patients developed *P. vivax* malaria.

Altogether, among these six patients there were eight malaria attacks, and primaquine dosing errors occurred in 8/16 (50.0%) primaquine prophylactic failures.

DISCUSSION

Malaria remains one of the most important infections worldwide, since the disease carries significant mortality and morbidity, especially if treatment is delayed.[5] Malaria prevention through chemoprophylaxis for travelers to endemic regions is a cornerstone of travel medicine, and recommendations for the use of primaquine in areas highly endemic for *P. vivax* exist in Israel and the United States.[3,6]

Primaquine was traditionally used in travelers for terminal prophylaxis (i.e., for postexposure eradication of hypnozoites in vivax/ovale malaria). Since 2006, it also became an agent for primary prophylaxis. Low dose of primaquine—15 mg base/day—is associated with increased likelihood of prophylaxis failure.[2] The recommended dose of primaquine was therefore raised and is currently 30 mg base/day.[3]

We have shown in this study that in Israel, half of malaria attacks because of primaquine prophylaxis failure were associated with low-dose primaquine attributed to human error, that is, prescription errors relating to the base/salt confusion. The error resulted from either the traveler's or the pharmacist's misapprehension, where it was assumed that the prescription

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TABLE 1
Cases of malaria occurring after primaquine prophylaxis

	Primaquine 15 mg base/day ($N = 6$)	Primaquine 30 mg base/day ($N = 8$)	P value*
Age (mean ± SD, years)	32.8 ± 10.6	32.4 ± 9.4	0.75
Gender (M/F)	5/3	4/2	1.00
Early (*Plasmodium falciparum*) malaria	2	4	0.60
Late (*P. vivax*) malaria	6†	4	

SD = standard deviation.
*Student's *t* test and Fisher's exact test used for continuous and categorical data, respectively.
†Two travelers had developed both *P. falciparum* and *P. vivax* malaria.

for 30 mg base/day should be approximated to 26.3 mg salt dose of the single tablet, without understanding the difference between the base and salt forms.

Preventable adverse drug events including prescription errors are an unfortunate but frequent occurrence in all healthcare scenarios: from intensive care units to ambulatory care.[7,8] Errors in prescription dosing or frequency constitute more than a quarter of all prescription errors in ambulatory care.[9] Serious prescription errors have also been documented in the treatment and prophylaxis of malaria.[10] However, what appears to be almost unique to primaquine is the importance of errors caused by the simultaneous labeling of base and salt forms.

By and large, modern pharmaceutical practice is to report dosing according to the active ingredient. In fact, in 2013, the USP had changed its monograph guidelines so that in new medication monographs, drugs will be described as their active, that is, base forms and not in their salt forms.[4] However, these guidelines do not apply to medications historically described in terms of both base and salt. This is the case, for example, for erythromycin, which exists as two oral forms: erythromycin ethylsuccinate and erythromycin base.

In the field of tropical diseases, many older medications in which salt/base dosing is still in use remain the mainstay of treatment. Pentamidine is currently an infrequently used agent in developed countries, but is used in developing countries for the treatment of leishmaniasis and human African gambiense trypanosomiasis. Pentamidine exist as two salt forms: isethionate and methanesulfonate, and original treatment guidelines discussed dosing according to the drug base equivalent. Confusion between salt and base doses had probably caused widespread dosing errors and underdosing of pentamidine, which in turn led to the erroneous perception of low pentamidine efficacy for leishmaniasis.[11]

In malaria prophylaxis and therapy, the anachronistic labeling practice of both base and salt is still common. This is because quinine, primaquine, chloroquine, and hydroxychloroquine are currently available, both in the United States and Israel, only in a single-salt form. Primaquine is marketed as a tablet of 26.3 mg primaquine phosphate, which is equivalent to 15 mg of primaquine base. Because the prophylactic and therapeutic dose of primaquine is 30 mg base, the likelihood for confusion is high, and may involve the prescribing physician, the issuing pharmacist, or the patient himself.

The efficacy of primaquine in primary malaria prophylaxis is not 100%. Fixed dose regimens may fail to protect large and overweight travelers.[12] Even with the correct dose, a few patients (also seen in our series) still develop malaria. In this respect, it is important to note that people with poor or intermediate activity of cytochrome P450 2D6 (~17% Israeli adults[13]) may not adequately metabolize primaquine to its active metabolite and thus become infected with malaria. However, dosing errors and underdosing can only compound and augment this problem.

The dual nature of the labeling of primaquine lends itself to misapprehension by physician, pharmacist, or patient. Adopting a single moiety, the base form, as the basis for all labeling and dosage guidelines would go even further toward eliminating dosage confusion for antimalarial agents, especially for primaquine.

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