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Utility of 8-Aminoquinolines in Malaria Prophylaxis in Travelers

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Abstract

Purpose of Review To review the current status of 8-aminoquinolines in the prophylaxis of malaria among travelers, in light of the recent approval of tafenoquine.

Recent Findings Primaquine continues to provide excellent primary prophylaxis against all *Plasmodium* species. Tafenoquine provides similarly good prophylaxis, with the benefit of weekly dosing. Both agents require glucose-6-phosphate dehydrogenase activity testing before use and are contraindicated in pregnancy. Pharmacodynamic variability relating to CYP2D6 may underlie some cases of primaquine failure; the effects of CYP2D6 on tafenoquine efficacy require further study.

Summary Tafenoquine and primaquine are the only current drugs that provide complete malaria prophylaxis, and should be considered the agents of choice in areas where both *P. vivax* and falciparum are frequent. Monthly tafenoquine is promising and should be further studied in travelers.

Keywords 8-aminoquinolines · Primaquine · Tafenoquine · *Plasmodium vivax* · *Plasmodium falciparum*

Introduction

Malaria presents one of the most formidable infectious risks faced by travelers to endemic countries. The WHO estimates that 219 million cases of malaria occurred worldwide during 2017. Globally, the last decade has seen an 18% decline in malaria rates; however, this decline had stalled in the last 3 years [1]. The overall number of travel-related malaria cases and of malaria deaths in the European region for example is stable or even increasing, reflecting the continued grown in international tourism [1]. Similar increases were also reported from the USA, with more than 2000 cases in 2016 [2].

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But while the need for malaria prevention is increasing, options for chemoprophylaxis have remained limited, with some older agents falling out of use because of widespread resistance, and others because of their adverse effect profile. This is why the 2018 FDA approval of a new 8-aminoquinoline: tafenoquine for malaria prophylaxis had created a resurgence of interest in this drug class.

The aim of this paper is to review the history of 8-aminoquinolines in the prevention of malaria in travelers, with a focus on the newest antimalarial drug: tafenoquine.

History of 8-Aminoquinolines: Pamaquine, Primaquine

Malaria is a neglected tropical disease; nothing attests this more than the fact that most current antimalarial agents were developed many years ago, usually as a result of wars in the tropics, and the 8-aminoquinolines are no exception. The first 8-aminoquinoline agent, Pamaquine, was synthesized in the 1920s in Germany and introduced by the British and Indian armies on a large scale for the treatment of malaria (in conjunction with quinine) during conflict in Burma [3]; this combined treatment regimen became routine by 1933 [4]. Most of the key insights on the effects of 8-aminoquinolines on different *Plasmodium* species and on the adverse effects of 8-aminoquinolines were made very soon after the introduction of pamaquine. These included:

a. The drug was not effective on the blood stage of *Plasmodium* and could not be used alone for the treatment of acute malaria.
b. However, if given in conjunction with quinine, the number of malaria relapses, especially *P. vivax*, was markedly reduced.
c. Pamaquine was a potent gametocidal agent and could thus have a role in malaria eradication programs.
d. The drug could be employed as a prophylactic agent with significant lowering of malaria attacks in troops.
e. However, its use was limited by frequent adverse reactions: severe and even fatal methemoglobinemia was dose-related and was of less concern once the dosing regimen was reduced; however, severe hemolytic reactions also occurred.

The advent of first quinacrine (mepacrine) and later of the 4-aminoquinoline chloroquine, both agents with better tolerability, led to abandonment of 8-aminoquinoline research until late stages of the Second World War. Renewed research resulted in the introduction of primaquine in the late 1940s. Primaquine was more potent than pamaquine and had all its above-mentioned advantages. During the Korean War, *P. vivax* malaria emerged as an important military concern, and while weekly chloroquine was used for field chemoprophylaxis, mass administration of primaquine to departing military personnel was employed, with the aim of aborting late relapses of *vivax* malaria. This "terminal prophylaxis" was administrated for 2 weeks, to coincide with the repatriation by sea of most troops, and became the basis of current protocols. It was also the use during the Korean War that led to further insight into the most alarming adverse effect of primaquine-hemolytic anemia. It became apparent that the risk of hemolytic anemia was much higher among African-Americans [5, 6]. However, the 15-mg 2-week regimen led to few fatalities in this population, and the regimen was unchanged and deemed safe. Even after the elucidation in the 1960's that glucose-6-phosphate dehydrogenase (G6PD) deficiency was the mechanism underlying hemolysis, no recommendations for screening prior to primaquine administration were made [7]. This complacency was unwarranted, because severe and fatal hemolytic reactions were recorded when primaquine was used in areas where non-African variants of G6PD were present, especially in the Mediterranean region, Middle East, and Southeast Asia. Although the focus during the Korean War was on the efficacy of primaquine against late relapses of *P. vivax*, additional trials on human volunteers have definitely shown that primaquine has a potent liver-stage effect on *P. falciparum* and can thus provide primary prophylaxis against all human plasmodia [8].

Thus, the main benefits, modes of utilization, and limitations of primaquine were established within a decade of its discovery. With the availability of chloroquine: an excellent, once-weekly, well tolerated *P. falciparum* prophylaxis, no further studies on primaquine as primary prophylaxis were performed for many years, and its prophylactic use was restricted to presumptive anti-relapse therapy (PART) for *P. vivax* malaria. In fact, recognition of the potential severity of hemolysis after primaquine, and the misconception that *P. vivax* malaria has a benign course ("benign tertiary"), resulted in a suggestion that rather than employ PART, the clinician should let *P. vivax* malaria "run its course" [9]. Few advances were made in the following decades, except dose changes and recognition of drug interactions. Interest in the utility of primaquine as primary prophylaxis against both *P. falciparum* and *P. vivax* malaria emerged in the 1990s, concomitant with worsening resistance to other antimalarials. Studies of primary prophylaxis in Irian Jaya [10], Colombia [11], and in Israeli travelers [12] have documented primaquine's very high efficacy against both pathogens, and against both primary and late relapse malaria.

Current Status of Primaquine

Current applications of primaquine for malaria are fourfold:

1. As a hypnozoiticidal treatment for *P. vivax* malaria, with the aim of preventing late relapses of the disease, i.e., "radical cure".
2. As a gametocidal agent for patients with *P. falciparum* malaria, with the aim of disrupting the further transmission of the pathogen to mosquitoes. The evidence base for this practice is more theoretical than experimental, as was concluded in a recent meta-analysis [13].
3. As PART (also termed "terminal prophylaxis") following prophylaxis with non-8-aminoquinoline antimalarials. It has been shown conclusively in travelers that even agents with liver schizonticidal activity such as atovaquone-proguanil do not affect liver hypnozoites and do not reduce late malaria [14].
4. As primary prophylaxis against all species of *Plasmodium*. In areas where high incidence of both *P. vivax* and *P. falciparum*, primaquine should be considered as the drug of choice for malaria prophylaxis.

Historically, *P. vivax* had been the dominant malaria species in some world regions (e.g., the Korean peninsula and the Amazon basin). In addition, even as malaria control efforts progress in many countries, rate reduction is often more prominent for *P. falciparum* and the relative proportion of cases caused by *P. vivax* is in fact increasing [15]. Thus, clinicians' motivation to utilize primaquine in malaria prophylaxis is likely to increase.

Several factors however may hinder the increased use of primaquine including poor availability, cost, and above all the

issue of G6PD deficiency. G6PD deficiency is x-linked and therefore males are more likely to be affected; however, due to X-chromosome inactivation, heterozygous women may also develop clinically significant hemolysis after exposure to primaquine. Quantitative G6PD assays are required to establish normal phenotype in women, and simple qualitative tests should only be utilized in men. These tests have significant turnover time and therefore prescribing primaquine to persons traveling on short notice is problematic [16]. Qualitative and more recently quantitative point of care G6PD activity assays have been developed, and may provide a solution for these cases, but require further study in the traveler population.

Despite many decades of use, primaquine still provides excellent prevention of relapse [17]. When primaquine failure is documented, multiple factors need to be reviewed, since there is little evidence of true resistance. It is possible that different strains require different doses of primaquine to ensure efficacy; for example, stains from Africa may require doses of 3.5 mg/Kg for cure whereas the Chesson strain may require 6 mg/Kg to ensure cure [14]. The current recommended dose of primaquine is 30 mg/Kg; this regimen ensures adequate primaquine dose for almost all patients. Issues of patient compliance and the inadvertent administration of low doses of primaquine (either in large/obese patients [14, 18] or because of dosing error relating to confusion between the salt and base forms of the drug [19]) may still underlie primaquine failure. Pharmacodynamics may also contribute to primaquine failure. The antimalarial effect of primaquine was only recently elucidated; it requires metabolic transformation in the host, with the production of hydroxylated primaquine metabolites: a process which is dependent on the activity of cytochrome P4502D6 (CYP2D6) [20]. CYP2D6 exists in multiple alleles that result in high, normal, or poor primaquine metabolism and activity. These appear to be associated with different success rates of radical cure and PART [21, 22].

Tafenoquine

The last 8-aminoquinoline antimalarial to enter clinical use is tafenoquine. It was as its predecessors the product of military medical research, in the late 1970s. Tafenoquine, which was already hailed in the late 1990's as the "antimalarial for the new millennium" [23], required 40 years before it became available for use for both treatment and prophylaxis of malaria. It is now available as two different brands approved for two different indications: as Krintafel© (GlaxoSmithKline) for the radical cure of *P. vivax* malaria, and as Arakoda© (60 Degrees Pharmaceuticals) for malaria prophylaxis [24].

Differences and Similarities with Primaquine In essence, tafenoquine is clinically similar to primaquine: it is effective against the liver stage of all *Plasmodium* species and inhibits hypnozoites of *P. vivax/ovale*. Thus, it provides good primary prophylaxis and radical cure after primary attack of relapsing malaria species. Clinical trials have shown good protective efficacy against malaria. It should be noted however that a large multicenter phase-3 trial failed to show non-inferiority of tafenoquine compared with primaquine, even though the dose of primaquine used (15 mg QD) was half the currently recommended dose [25]. Thus, the possibility that primaquine has a slightly superior efficacy has not been ruled out and needs to be further explored.

Tafenoquine's most appealing characteristic is its pharmacokinetic profile (Table 1) which results in an extremely long half-life of 15 days, whereas primaquine requires daily administration. Tafenoquine can thus be expected to have improved compliance. For radical cure as well as for PART, a single dose of tafenoquine represents a complete course of therapy. Tafenoquine is currently approved as a weekly dose for malaria prophylaxis. However, monthly administration had shown high protective efficacy [26, 27]. For many short-

Table 1 Selected pharmacodynamic/pharmacokinetic parameters of 8-aminoquinolines

	Primaquine	Tafenoquine
Absorption/dietary	Fatty meals↑	Fatty meals↑
Distribution (Vd)	150–250 L	1600–2470 L
Protein binding	75%	> 99.5%
Time to peak	1–3 h	12–5 h
Elimination half-life	3.7–9.6 h	15–16.5 days
Metabolism/transport	CYP2D6 dependent	CYP2D6?[a]
Excretion	Renal	Gastrointestinal
Drug interactions	CYP2D6, MATE1, OCT2 substrates	MATE1, OCT2 substrates
Trans placental penetration	+	+
Excretion in breast milk	Small amounts	Small amounts

[a] Animal data suggests CYP2D6 is required for anti-relapse effects of tafenoquine; however, little human data exist

Vd, volume of distribution; *CYP2D6*, cytochrome P450 isoenzyme 2D6; *MATE1*, multidrug and toxin extrusion 1; *OCT2*, organic cation transporter 2

term travelers, monthly prophylaxis could have created the possibility to provide simple, pre-travel malaria prophylaxis, thereby eliminating completely the whole issue of compliance. The reasons why the drug's developers chose not to further pursue this regimen are unclear.

The full adverse effect profile of tafenoquine is still unknown. However, its main limitation is similar to that of primaquine—the need the exclude G6PD deficiency prior to use. The hemolytic potential of both drugs was similar in heterozygous Thai women [28]: it should be kept in mind, that experience with tafenoquine in persons with the severe Mediterranean variants of G6PD deficiency is lacking, and additional caution is required. The need for G6PD testing significantly limits the ability to utilize tafenoquine in last-minute travelers.

Although the efficacy of tafenoquine as malaria prophylaxis was very good, its efficacy in diverse ethnic populations could vary according to CYP2D6 activity. In mice, CYP2D activity is essential for tafenoquine activity; however, human metabolism is not identical. Retrospective analyses of clinical data have suggested that at least the intermediate metabolizer profile is not associated with increased clinical failure [29]; further data is essential as the numbers studied were small and did not include poor CYP2D6 metabolizers.

8-Aminoquinolines for Malaria Prophylaxis in Travelers: Comparison to Other Agents

Considering all these data, how do 8-aminoquinolines compare with other agents (Table 2)? Atovaquone-proguanil is currently the preferred agent for many travelers, due to its benign adverse effect profile and its ability to provide liver-stage prophylaxis for *P. falciparum*. In recent years, off-label modifications that further simplify the regimen of atovaquone-proguanil (twice-weekly administration and discontinuation 1 day rather than 7 days after return from travel) were evaluated in travelers and appear to be effective [33–35]. Older agents are associated with significant neuropsychiatric adverse events (mefloquine) [36] or require both daily dosing and an additional month post-departure from endemic areas (doxycycline). Also, older agents do not protect against relapsing malaria species. Primaquine, while offering complete prevention to all forms of malaria, requires daily dosing. Tafenoquine overcomes this problem, but its weekly dosing regimen does not present a major improvement on twice-weekly atovaquone-proguanil. Monthly tafenoquine could have created a major improvement: providing the traveler has time to undergo G6PD testing, simple pre-travel dosing for up to a month of travel becomes possible, obviating all concerns of compliance, while also being a simple option for the long-term traveler or expatriate to malaria endemic countries.

Table 2 Comparisons of 8-aminoquinoline drug regimens to atovaquone-proguanil regimens for malaria prophylaxis

Regimen	Atovaquone-proguanil (standard regimen) Daily	Atovaquone-proguanil (off-label regimen) [30] Twice weekly	Primaquine regimen Daily	Tafenoquine (standard regimen) Weekly	Tafenoquine (off-label regimen)[a] Monthly
№. of tablets required for 30 days of travel	38	10	76	16	12
Loading dose	No	No	No	Yes	Yes
Required dosing post travel	7 days	No	7 days	No	No
Plasmodium spp. prevention					
P. falciparum	Yes	Yes	Yes	Yes	Yes
P. vivax/ovale hypnozoites	No	No	Yes	Yes	Yes
P. malariae	Yes [b]	Yes [b]	Yes	Yes	Yes
Specific populations					
Pregnancy	Suggested safe (limited data) [c]	Not studied	Contraindicated	Contraindicated	Contraindicated
Breastfeeding	> 5 Kg	> 5 Kg	After G6PD testing for infant	After G6PD testing for infant	After G6PD testing for infant
Infants	> 5 Kg	Not studied	Yes	Not approved	Not approved
Renal failure	Creatinine clearance > 30 ml/min	Creatinine clearance > 30 ml/min	Limited data suggest safety	No data: not recommended	No data: not recommended

[a] Protocol as per Walsh et al. [26]

[b] *P. malariae* prophylaxis failure with atovaquone-proguanil has been documented [31]

[c] Although atovaquone-proguanil is not approved for use during pregnancy, data suggest its safety [32]

Conclusions

For nearly a century, the 8-aminoquinolines have remained unique among antimalarials in their ability to provide both causal and anti-relapse malaria prophylaxis. Thus, they are the only antimalarials that provide complete malaria prevention and should be considered the agents of choice in areas of high *P. vivax* and *P. falciparum* incidence [37–39]. Daily primaquine provides excellent prophylaxis in travelers and is generally well tolerated, once G6PD deficiency had been excluded. Tafenoquine, approved in 2018, is similarly effective and well tolerated, and has the benefit of weekly as opposed to daily administration. Its likely utility as a monthly agent requires further study.

Compliance with Ethical Standards

Conflict of Interest All authors declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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