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Invited Review

Primaquine revisited six decades after its discovery

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ABSTRACT

Primaquine was firstly synthesized in 1946 in the USA, and is the most representative member of the anti-malarial 8-aminoquinolines. Six decades have passed and primaquine is still the only transmission-blocking anti-malarial clinically available, displaying a marked activity against gametocytes of all species of human malaria, including multi-resistant *Plasmodium falciparum* strains. Primaquine is also effective against all exoerythrocytic forms of the parasite and is used in conjunction with other anti-malarials for the treatment of *vivax* and *ovale* malaria. However, primaquine is often associated with serious adverse effects, in consequence of its toxic metabolites. 5-Hydroxyprimaquine or 6-methoxy-8-aminoquinoline has been considered to be directly responsible for complications such as hemolytic anemia. Primaquine toxicity is aggravated in people deficient of 6-glucose phosphate dehydrogenase or glutathione synthetase. Adverse effects are further amplified by the fact that primaquine must be repeatedly administered at high doses, due to its limited oral bioavailability. Over the last two decades, Medicinal Chemists have battled against primaquine's disadvantages, while keeping or even improving its unequalled performance as an anti-malarial. The present text revisits primaquine and its properties on the occasion of its 60th anniversary and aims to give a general overview of what has been the path towards the development of effective and safe primaquine-based anti-malarials. Presently, aablaquine and tafenoquine the two most promising primaquine analogues are already in the final stages of clinical trials against *Plasmodium vivax* and *P. falciparum*. Both compounds are a new hope against malaria and other primaquine-sensitive illnesses, such as Pneumocystis Pneumonia or the Chagas disease.

1. Primaquine revisited

1.1. Historical synopsis

Tropical diseases, normally confined to underdeveloped regions of the globe, have been traditionally neglected by the pharmaceutical industries and, consequently, seldom considered as hot matter capable of drawing the attention of top scientists, from chemists to physicians. This attitude was changed by force of historical events in some periods, such as the first half of the 20th century, when world-wide belligerency required western soldiers, fighting in tropical regions, to be protected against this epidemics [1,2]. Consequently, in the 30 years' gap between the middle of World War I and the end of World War II was examined a huge number of potential anti-malarial drugs, over 12 000 of which were 8-aminoquinolines (8AQ) [3]. One of the first anti-malarial 8AQs, known as pamaquine or plasmochin (**1**), was synthesised in 1925 and was able to destroy the parasite's gametocytes when used in combination with quinine. This was useful for the prevention of relapses associated to the *Plasmodium vivax* infection [4], but pamaquine showed little effectiveness against blood-induced infection, i.e., it was a poor blood-schizontocide. But the greatest disadvantage of this drug was its high toxicity that ultimately led to the abandonment of its therapeutic use [5]. Notwithstanding, pamaquine represented the stepping-stone for the development of safer anti-malarial 8AQs that culminated, in 1946, in the synthesis of the 8AQ SN-13,272 by Elderfield and co-workers, in the United States of America [6]. This compound, named primaquine (PQ, **2**), was successfully tested in WWII prisoners, American volunteers and American soldiers fighting in regions like Korea [6]. Other anti-malarial 8AQs, such as pentaquine or isopentaquine [7–9], also appeared in the 1940s, but PQ was the one presenting the highest efficacy and the lowest toxicity levels.

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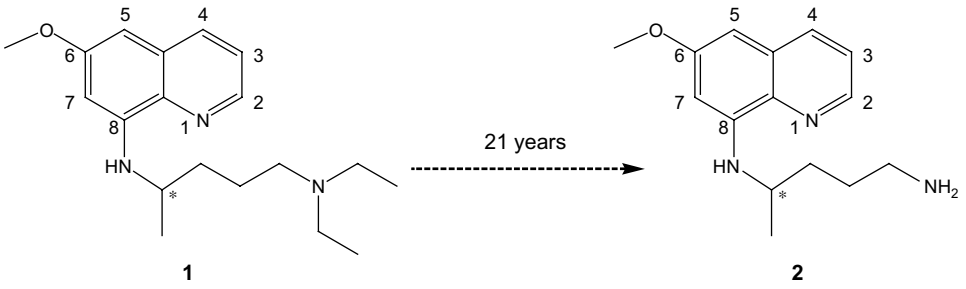

By the end of WWII, strategies for malaria treatment passed by the employment of PQ, primarily as a transmission-blocking anti-malarial (gametocytocide) but also as a tissue-schizontocide, as well as of chloroquine (CQ), a potent blood–schizontocidal 4-aminoquinoline (4AQ), also effective against the most lethal *Plasmodium falciparum* strains [10]. This, and the use of DDT against the mosquito vectors, led to the eradication of malaria from tempered and sub-tropical regions of the globe by the early 1960s, which cooled the interest of developed countries in continuing the search for improved anti-malarials, even though some problems associated with current therapies were already being identified in endemic areas like Sub-Saharan Africa [10]. Some of these problems included the aggravated hematotoxicity of PQ in humans deficient in 6-glucose phosphate dehydrogenase (6GPD), a genetic condition frequent among African men, and the development of general resistance of *P. falciparum* against CQ [10]. Again, these problems were mainly restricted to tropical countries and did not captivate the interest of either the western pharmaceutical industry or the scientific community until the 1980s, when some cases of malaria were registered in sub-tropical and tempered areas [11] "Imported malaria" is presently a serious risk world-wide due to both increased people's migration or tourism-related mobility and global warming. It is a top-priority disease and composes the WHOs "big-three" together with tuberculosis and AIDS [11]. This sprang a new search for more active and safer anti-malarials over the last two decades, much of it inspired in PQ and related 8-aminoquinolines [12,13].

1.2. A snapshot of PQ's therapeutic profile

1.2.1. Against malaria: use, limitations and search for alternative administration strategies

PQ is useful to fight malaria on three different fronts: (i) primary prophylaxis against all species of malaria, (ii) presumptive anti-relapse therapy (terminal prophylaxis) for persons extensively exposed to *P. vivax* or *Plasmodium ovale*, (iii) radical cure in individuals infected with *P. vivax* or *P. ovale* [14]. In endemic regions, PQ is used as a gametocytocide to prevent the transmission of the infection from the human host to the mosquitoes, thus blocking the spread of the disease [15].

Normally, a total of 200 mg dose of PQ (as the free base ≈ 350 mg of the phosphate salt) leads to a full cure. The regimen usually adopted and generally well-tolerated is 15 mg per day over 14 days [9,14]. Table 1 summarises the different PQ-based therapeutic approaches, according to the acuteness of the infection. PQ is contraindicated for children under 4 years old and its administration requires a previous test for glucose-6-phosphate activity (G6PD) in the patient [16]. PQ is not suitable to be used as a single drug to treat malaria, as it is not effective against endo-erythrocytic forms of *Plasmodia*, thus must be co-administered with blood-schizontocides [9].

The reappearance of malaria *vivax* in certain regions of the world by the end of the 20th century reinforced the relevance and the need of finding more effective treatments for the disease. An inadequate attack on the hypnozoite reservoir of infection can contribute to the aggravation of malaria. Ideally, PQ should be a well-tolerated drug and a totally safe drug of easy administration, so it could be employed at higher doses without risk for the patient (cf. Section 2). However, further from the aforementioned problems related to PQ-based therapies, PQ is not prescribed during pregnancy because of the risk of intravascular hemolysis in the mother and fetus [17]. Recently, changes in the platelet count and lipid parameters are reported for malarial patients after treatment with hydroxychloroquine and PQ for acute *P. vivax* malaria [18].

To circumvent problems associated with PQ, some researchers have proposed high-dosages over short administration periods, whereas others have recommended the use of quinine while assessing the efficacy of PQ at either standard or experimental PQ

Table 1
PQ-based therapeutic approaches against *vivax* and *ovale* malarias

Therapeutic approach	Description
Primary prophylaxis	Prevents primary installation of parasitemia, in opposition to terminal prophylaxis that prevents relapse (see below). A daily 30 mg dose (adult) is used and the administration begins one day before the risk of exposition, i.e., arrival to a malaria-endemic region, and is prolonged for 1 week after departure from that region. For children and adults under 60 kg of weight, the recommended dose is 0.5 mg/kg/d [14].
Terminal prophylaxis or PART	Presumptive anti-relapse therapy (or terminal prophylaxis) uses medications towards the end of the exposure period (or immediately thereafter) to prevent relapses or delayed-onset clinical presentations of malaria caused by hypnozoites (dormant liver stages) of *P. vivax* or *P. ovale* [14]. PQ is used in conjugation with a schizontocide (chloroquine, mefloquine, doxycycline) at a recommended daily dose of 15 mg PQ during 14 days (adults). However, full elimination of hypnozoites of some *P. vivax* strains requires an increase of the daily dose to 30 mg. Similarly, the paediatric doses can be increased from 0.25 to 0.5 mg/kg/d, according to the parasite strain that prevails at the site of exposure. The beginning of terminal prophylaxis with PQ should coincide with the last 2 weeks of prophylactic administration of schizontoxides doxycycline, mefloquine or chloroquine or with the final week of prophylaxis with atovaquone–proguanil [14,19,20].
Radical cure	PQ is administered together with a blood-schizontocide (e.g., chloroquine) for complete cure of installed *P. vivax* and *P. ovale* infections with the advantage that PQ can prevent relapses due to hypnozoites of both strains, as described above. Recommended PQ dosage is the same as described for terminal prophylaxis [14,21–23].