Challenges in the development of antimalarial drugs with causal prophylactic activity

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Introduction
There is a continuing need for improved drugs for treatment and prevention of malaria. Drugs with causal prophylactic activity are especially useful for prevention of malaria in individuals with a limited duration of exposure in a malaria-endemic area. In this paper I compare the requirements for causal prophylaxis of relapsing and non-relapsing malarias and review some of the challenges to the development of new prophylactic antimalarial drugs.

Terminology
The terminology of malaria infections and their treatment can be confusing but is important for the understanding of the expectations placed upon new antimalarials (see Table 1). The human portion of the malaria parasite life-cycle involves invasion of sporozoites into hepatocytes followed by parasite differentiation into hepatic (tissue) schizonts. Mature hepatic schizonts release merozoites that invade erythrocytes and then differentiate into erythrocytic (blood-stage) schizonts. Merozoites released from mature erythrocytic schizonts invade other erythrocytes to continue the asexual erythrocytic cycle that is responsible for clinical manifestations of malaria.

Drugs that kill parasites as they differentiate and develop in the liver are referred to as tissue schizontocides. Drugs that kill parasites as they differentiate and develop within erythrocytes are referred to as blood schizontocides. Drugs that eliminate all parasites from the body and thus prevent recurrent parasitemia are said to provide a radical cure.

For Plasmodium falciparum and P. malariae, there is only one form of hepatic parasite that develops after sporozoite inoculation. During the first 6 days after inoculation of P. falciparum sporozoites (FAIRLEY, 1945), this population of parasites develops into pre-erythrocytic schizonts, and these developing parasites are susceptible to a variety of tissue schizontocidal drugs. Radical cure can be achieved either by treatment with a tissue schizontocide during pre-erythrocytic development (causal prophylaxis), or by treatment with a blood schizontocide for a sufficient period after erythrocytic infection (suppressive prophylaxis). For P. vivax and P. ovale, there are 2 forms of hepatic parasites that develop after sporozoite inoculation. During the first 8 days after inoculation of P. vivax sporozoites (FAIRLEY, 1945), one population of parasites develops into pre-erythrocytic schizonts that are susceptible to a variety of tissue schizontocidal drugs. The other population of parasites, referred to as hypnozoites (KROTOSKI, 1985), remains dormant for months or years until the hypnozoites develop into pre-erythrocytic schizonts and these developing parasites are susceptible to a variety of tissue schizontocidal drugs. The hypnozoites can be killed by treatment with a tissue schizontocide during pre-erythrocytic development (causal prophylaxis), or by treatment with a blood schizontocide for a sufficient period after erythrocytic infection (suppressive prophylaxis).

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zoites. Thus the hurdle for a drug to have useful causal prophylactic activity is greater for \(P. \) \textit{vivax} than for \(P. \) \textit{falciparum}.

**Animal models of causal prophylaxis**

Both rodent and primate models have been used to screen drugs for causal prophylactic activity (FINK, 1974; PETERS et al., 1975; DAVIDSON et al., 1981). The rodent models are amenable to high-volume screening and, by comparing the response to sporozoite-induced and blood-induced infections, they can detect tissue schizontocidal activity for drugs that also have blood schizontocidal activity. However, rodent parasites do not have a hypnozoite stage in their life-cycle, whereas \(P. \) \textit{cynomolgi} used in the primate model does. Drugs that have no causal prophylactic activity against \(P. \) \textit{falciparum} or \(P. \) \textit{vivax} are inactive in both rodent and primate models of causal prophylaxis. Drugs that have causal prophylactic activity against \(P. \) \textit{falciparum} but not \(P. \) \textit{vivax} are active in the rodent models but not the primate model, and drugs that have causal prophylactic activity against \(P. \) \textit{vivax} are active in the primate model. Thus the rodent models are useful for identifying compounds that may have causal prophylactic activity against \(P. \) \textit{falciparum} and are worthy of further evaluation in the primate model. The primate model is useful for the identification of compounds that may have radical curative activity against \(P. \) \textit{vivax}.

The major classes of drugs that have been shown to have causal prophylactic activity in the rodent models are antifolate drugs, naphthoquinones, and 8-aminoquinolines (PETERS et al., 1975). Only 8-aminoquinolines and (to a lesser extent) 6-aminoquinolines have activity in the primate model (DAVIDSON et al., 1981).

**New agents in clinical development with causal prophylactic activity**

Primaquine is an 8-aminoquinoline (see Figure) that is effective for radical cure of most \(P. \) \textit{vivax} infections, but it can cause severe haemolytic anaemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency (BREWER & ZAEAFONETIS, 1967).

WR 238605 is a newer 8-aminoquinoline (see Figure) with greater potency than primaquine in both the rodent and primate models of causal prophylaxis and with lower toxicity (PETERS et al., 1993; BRUECKNER et al., 1998b). In a clinical pharmacokinetics study, WR 238605 was generally well tolerated, with gastrointestinal side-effects occurring in some patients receiving higher doses. Plasma drug concentrations increased linearly over the doses studied, with a long absorption phase \((T_{\text{max}}=12 \text{ h})\) and a long elimination half-life \((14 \text{ days})\) (BRUECKNER et al., 1998b). The long elimination half-life suggests that single-dose treatment with WR 238605 may be effective for elimination of hypnozoites to achieve radical cure in \textit{vivax} malaria. WR 238605 also appears to have causal prophylactic activity against \(P. \) \textit{falciparum} (BRUECKNER et al., 1998a) and thus may be useful for prophylaxis in travellers. However, repeated administration of high doses of WR 238605 has been associated with haemolysis in individuals with G6PD deficiency (W. Milhous, personal communication). An important challenge will be to determine whether a lower dose can be identified that is safe for use in G6PD-deficient individuals.

![Figure. Structures of WR 238605, primaquine, atovaquone and proguanil.](https://academic.oup.com/trstmh/article-abstract/92/6/577/1924573/7a950515e5055711243548c5a29d99e9)
Malarone™, a fixed-dose combination of atovaquone and proguanil hydrochloride (see Proguanil), is a new antimalarial that is approved in more than 25 countries for treatment of uncomplicated malaria caused by P. falciparum (RADLOFF et al., 1996; DE ALENCAR et al., 1997; LOOAREESUWAN et al., in press). The combination of atovaquone and proguanil hydrochloride is also highly effective for prevention of falciparum malaria in Africa (LELL et al., 1998; SHANKS et al., 1998). Atovaquone is a hydroxynaphthoquinone that inhibits mitochondrial electron transport and is active as both a blood schizonticide and a tissue schizontocide (DAVIES et al., 1989). It is the most hypnozoite-specific drug available (LOOAREESUWAN et al., 1996) but does have causal prophylactic activity against P. falciparum. In volunteers challenged by the bites of sporozoite-infected mosquitoes, parasitaemia developed in all 4 control subjects who received placebo, but parasitaemia was prevented in all 6 subjects who received a single dose of 250 mg atovaquone 1 day before challenge (T. Shapiro, personal communication). On days 6 and 7 after challenge, when merozoites released from hepatic schizonts would first be expected to invade and replicate within erythrocytes, sensitive methods to detect blood-stage parasites by culture and polymerase chain reaction (PCR) failed to detect parasitaemia. Higher doses of atovaquone are not consistently effective for treatment of blood-stage infection (CHIODINI et al., 1995), and plasma levels of atovaquone on day 6 and 7 were below the minimum inhibitory levels for blood-stage parasites. These results indicate that atovaquone, like proguanil, has causal prophylactic activity against P. falciparum.

One of the major challenges for newly developed drugs with causal prophylactic activity against P. falciparum will be the challenge to the prevailing concept that post-exposure prophylaxis must always be continued for at least 4 weeks after leaving a malaria-endemic area. The pre-erythrocytic stages of P. falciparum appear to be more sensitive than asexual erythrocytic stages to proguanil (COVELL et al., 1949), cycloguainil (LUNNS et al., 1964) and atovaquone (T. Shapiro, personal communication). Studies with proguanil demonstrated that starting treatment at least 1 day before and continuing for 6 days after the bites of malaria-infected mosquitoes provides consistent protection against parasitaemia (FAIRLEY, 1946; COVELL et al., 1947). I am aware of no data that suggest that the continuation of post-exposure prophylaxis with proguanil for longer than 6 days provides additional benefit. Despite this, it is often recommended that proguanil be continued for 4 weeks after returning from a malaria-endemic area (WHO, 1997).

The availability of a combination therapy containing atovaquone and proguanil, both of which have causal prophylactic activity against P. falciparum, offers an opportunity for simplifying the management of malaria prophylaxis in travellers.

References


