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 antimalarial drugs. 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 parasitaemia 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 capable of initiating a blood-stage infection (relapse). Neither causal prophylaxis (using a drug that acts only on dividing hepatic parasites) nor suppressive prophylaxis is able to achieve radical cure of these relapsing parasites. Radical cure of relapsing malarias must include a drug that is able to destroy hypnozoites.

Causal prophylaxis of falciparum malaria
Studies reported by FAIRLEY (1945) demonstrated that, 7 min after being bitten on one arm by a P. falciparum-infected mosquito, 200 mL of blood obtained from the other arm was able to transmit infection to a naive volunteer. This is attributable to circulating sporozoites that have not yet invaded hepatocytes. From 30 min after being bitten, and continuing for the next 6 days, subinoculations were negative. From day 7 onward subinoculations were positive. When volunteers were treated with mepracrine (Avebrine™) at a dose of 100 mg daily, starting before infection and continuing for several weeks after, subinoculations were positive with blood collected on days 1, 8 or 9, even though parasites could not be demonstrated in thick smears, but subinoculations were negative by day 11 or 12. If mepacrine was continued at this dose for 23 days after infection, P. falciparum infections were cured, and the blood never regained infectivity. The interpretation of these studies is that mepacrine has suppressive prophylactic activity but not causal prophylactic activity against P. falciparum. Similar results have been obtained with other blood schizontocides such as quinine, chloroquine and mefloquine.

In contrast to the results with mepacrine, proguanil was shown to have causal prophylactic activity against P. falciparum (FAIRLEY, 1946). Volunteers treated with 100 mg proguanil daily from day -1 to 123 after sporozoite-induced infection did not develop malaria, and subinoculations on day 7 were negative in volunteers treated with proguanil but positive in control volunteers treated with mepacrine. Single doses of 100 mg proguanil on day +2, or single doses of 25, 50 or 100 mg proguanil on day +3, day +4 or day +5, consistently achieved cure of sporozoite-induced P. falciparum infections. Single doses of 100 mg proguanil on day 0, day +1 or day +6 or beyond did not prevent parasitaemia. These results indicate that proguanil has causal prophylactic activity directed against the hepatic stages of P. falciparum. Subsequent studies with another P. falciparum strain confirmed that 50 or 100 mg proguanil given from shortly before until 6 days after sporozoite challenge provided complete causal prophylaxis (COVELL et al., 1949). If proguanil was started after blood-stage infection was present, cure was not achieved consistently with 100 mg proguanil daily for 7 days, indicating that pre-erythrocytic forms of P. falciparum are more susceptible to proguanil than are asexual erythrocytic parasites. Cycloguanil (the active metabolite of proguanil) and pyrimethamine (another antifolate drug) also have tissue schizontocidal activity against P. falciparum (BRAY & BURGESS, 1959; LUNN et al., 1964).

Causal prophylaxis of vivax malaria
For P. vivax, a distinction must be made between tissue schizontocidal activity and causal prophylactic activity. Volunteers treated with 1000 mg proguanil daily for 14 days after sporozoite-induced P. vivax infection had a delayed time to their first episode of parasitaemia but relapsed after 29–86 days (FAIRLEY, 1946). Pyrimethamine also has tissue schizontocidal activity against P. vivax (COATNEY et al., 1953) and the relapsing primate parasite P. cynomolgi (EYLES & COATNEY, 1946) but does not prevent late relapses. This indicates that antifolate drugs have tissue schizontocidal activity against actively replicating pre-erythrocytic hepatic stages of P. vivax but not against the dormant hypo-
zoites. Thus the hurdle for a drug to have useful causal prophylactic activity is greater for *P. vivax* than for *P. 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. cynomolgi* used in the primate model does. Drugs that have no causal prophylactic activity against *P. falciparum* or *P. vivax* are inactive in both rodent and primate models of causal prophylaxis. Drugs that have causal prophylactic activity against *P. falciparum* but not *P. vivax* are active in the rodent models but not the primate model, and drugs that have causal prophylactic activity against *P. vivax* are active in the primate model. Thus the rodent models are useful for identifying compounds that may have causal prophylactic activity against *P. 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. 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. vivax* infections, but it can cause severe haemolytic anaemia in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency (Brewer & Zarefianitis, 1967).

WR 238605 is a new 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_max=12 h) and a long elimination half-life (14 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 vivax malaria. WR 238605 also appears to have causal prophylactic activity against *P. 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](https://academic.oup.com/trstmh/article-abstract/92/6/577/1924573)

**Figure.** Structures of WR 238605, primaquine, atovaquone and proguanil.
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., 1996). Proguanil provides additional benefit. Despite this, it is often recommended that proguanil be continued for 4 weeks after prophylaxis with proguanil for longer than 6 days prophylaxis in travellers.

References


