REVIEW ARTICLE

Tafenoquine: A New 8- Aminoquinoline

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INTRODUCTION

Malaria remains one of the major health hazards, with high associated morbidity and mortality in addition to having a crippling effect on the economy. Worldwide, malaria is the cause of morbidity in 300-500 million people annually, out of whom, 2-3 million die[1]. The disease is endemic within most tropical and subtropical regions of the world but 90% of all malaria deaths currently occur in Sub-Saharan Africa. In Africa, official figures show that a child dies of malaria every 45 seconds and the disease is responsible for 20% of all childhood deaths[2]. In Zambia, an estimated 3 million cases are said to occur every year and in the year 2006, the estimated number of deaths because of the disease was 6,484 [3] .The parasites responsible for malaria include P. falciparum, P. vivax, P. ovale and P. malariae. P. vivax and P. ovale exhibit the exoerythrocytic stage responsible for relapses, but of critical importance in Sub-Saharan region is P. falciparum.

P. falciparum has become resistant to chloroquine rendering chloroquine unreliable for both chemoprophylaxis and treatment of Malaria in P. falciparum endemic Sub-Saharan region including Zambia. To overcome this problem, it is important to interrupt the transmission of malaria. Chemoprophylaxis, in endemic areas, is recommended for pregnant women and for those at high risk of severe malarial disease (e.g. severe anemia). It is also important for healthy travelers prior to visit to endemic areas. Antimalarial chemoprophylaxis currently relies on mefloquine, doxycycline and chloroquine for blood stage (suppressive) prophylaxis and primaquine and atovaquone-proguanil (Malarone) for liver stage (causal) prophylaxis [4].

A chemoprophylactic drug should, ideally, be taken infrequently to improve compliance and it should be very well tolerated and highly efficacious against all species of malaria. Primaquine eliminates the need for continued intake after the termination of exposure, in contrast to drugs active only against blood stages. For P.vivax, there has been very little focus with regards to identification of new family of compounds active against the hypnozoites. Primaquine, an 8-aminquinoline, has been the main stay therapy for past 60 years for clearing parasites from the liver. However, primaquine has a low therapeutic index, is associated with serious side-effects, has a short half-life and daily dosing is needed [5]. Tafenoquine, also known as WR238605, is a new 8- aminoquinoline which was synthesized to overcome deficiencies of primaquine. It has the potential to replace it as a prophylactic agent, since it has a much longer half-life, better therapeutic index and greater activity against both the blood and liver stages of malaria [4].

CHEMISTRY

Tafenoquine (±) -8- (4–amino-1-methylbutyl) amino - 2,6 - dimethoxhy-4 methyl - 5 - (3-trifluoromethylphenoxy) quinoline succinate}is a primaquine analogue.

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PHARMACODYNAMIC PROPERTIES AND ANTI-MALARIAL ACTIVITY

Degradation of hemoglobin by malarial parasite generates heme which is toxic to the parasite. Heme is then detoxified by the parasite itself through its conversion into insoluble pigment, hemozoin. Tafenoquine accumulates within the food vacuoles and inhibits the detoxification of heme to hemozoin by the malarial parasite. It does so by inhibiting hematin polymerization by binding to its -oxo dimer, thus inhibiting the formation of hemozoin, which consists of cyclic heme dimers arranged in an ordered crystalline structure through intermolecular hydrogen bonding. Tafenoquine, via its hydroxylated metabolites, stimulates the hexose monophosphate shunt, increases methemoglobin production and decreases glutathione levels in the cells. The pro-oxidant properties of its metabolites correlate with its exoerythrocytic schizontocidal action and also contribute to its erythrocytic schizontocidal action [6].

Tafenoquine, in vitro, also demonstrates gametocidal and sporontocidal activity suggesting a potential role in blocking of transmission[7]. In preclinical studies, tafenoquine demonstrated 3-67 times higher blood and tissue schizontocidal activity than primaquine. In vitro studies also demonstrated an apparent synergism of blood schizontocidal activity with chloroquine and artemisinin [8].

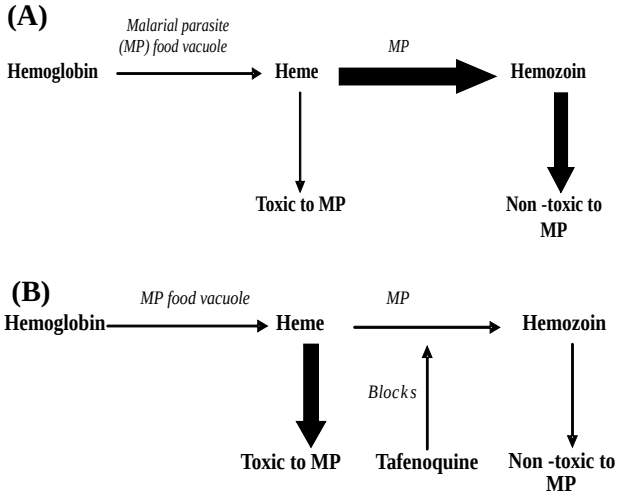

Fig.1: Inhibitory Effects of Tafenoquine (B) on Heme Detoxification (A) by Malarial Parasite.

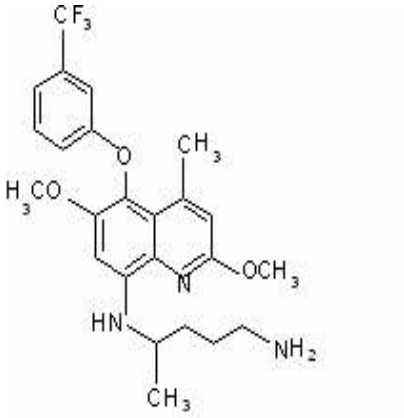

Fig. 2: Structure of Tafenoquine

PHARMACOKINETIC PROPERTIES

In a phase I study in which a single dose was given to fasting subjects, linear kinetics was demonstrated at a dose of 400-600 mg base. On administration of 600 mg to healthy volunteers as a single dose, peak blood concentration of 417-489 ng/ml were observed[9]

In a study done on Thai soldiers, minimum steady state concentration of 80-100 ng/ml were achieved with a loading dose of 1200 mg (400 mg/day for 3 days) followed by monthly dose of 400 mg for 5 months. The mean value of apparent volume of distribution seen was 1820 L. A standard high-fat meal has been found to increase its bioavailability by 40% [9].

Unlike primaquine, tafenoquine was also found to accumulate in red blood cells, with a whole blood to plasma concentration ratio of close to 1.8. Such accumulation may contribute to the greater potency of tafenoquine compared with primaquine [10].

TOLERABILITY

In clinical trials, oral tafenoquine was well tolerated, with only mild and transient gastrointestinal disturbances reported as possible side effects [4].

In a double blind chemoprophylaxis trial in adult residents of Ghana, physical complaints involving the musculoskeletal, gastrointestinal and respiratory systems collectively accounted for 52%-70% of the total adverse events prompting health clinic visits.

The common events recorded included: Gastrointestinal ADRs like abdominal pain, gastritis, diarrhea; Musculoskeletal ADRs like backache, myalgia, polyarthralgia/arthralgia; as well as respiratory tract complaints including sore throat [11,12].

No trial, has reported dose-related adverse events so far. In the trial conducted in Kenya for prophylaxis against P. falciparum, dermatological events of mild to moderate severity were reported. Two hemolytic events also occurred during this study in volunteers who were later found to be glucose-6-phosphate dehydrogenase (G6PD) deficient [12].

Abnormal elevation of alanine amino transferase (ALT) level to more than 60 U/l has been reported in one of the trials [11]. Slight reduction in levels of haemoglobin was reported in trials conducted in endemic areas of Gabon and Ghana. These findings were, however, not found to be dose related [11].

CAUTION

It should not be prescribed to G6PD deficient patients and in pregnancy.

THERAPEUTIC TRIALS

The first clinical study to report its prophylactic efficacy against P. falciparum malaria was done using a human challenge model in which volunteers were exposed to mosquitoes infected with a chloroquine sensitive clone (NF 54) of P. falciparum. A single 600 mg oral dose successfully prevented P. falciparum malaria in three of four non-immune volunteers in this challenge model [10]. In clinical studies in western Kenya, where P. falciparum is holoendemic, tafenoquine given weekly at a dose of 200 and 400 mg provided protective efficacies of 86% and 89% respectively. An important observation in this trial was that, a 3-day treatment regimen of tafenoquine 400 mg/day, followed by a weekly placebo, protected 82% participants for 7 weeks after commencement of drug administration [9].

The prophylactic value of tafenoquine was further demonstrated in clinical studies in Ghana and Gabon, with protective efficacies of more than 86% using lower dose regimens of tafenoquine, such as 200 mg weekly [11]. A randomized, placebo controlled study showed that after a loading dose of tafenoquine 400 mg/day for 3 days followed by 6 months of single monthly doses of tafenoquine 400 mg, the drug was 96% and 100% effective in preventing P. vivax and multi drug resistant P. falciparum malaria, respectively [13]. In operational deployments in Thailand, tafenoquine as a single 600 mg dose prevented P. vivax relapse in a follow up of 8 weeks (protective efficacy of 92.6%) [14].
Presently a safety study is being carried out to allow a phaseII/III efficacy study to start in 2010 [5].

DOSE

As a prophylactic agent tafenoquine has been found to be significantly effective at doses ranging from 600 mg as a single dose to 1200 mg as loading dose (400 mg/day for 3 days) followed by monthly doses of 400 mg [4]. The recommended dosage for chemoprophylaxis of malaria, awaits conclusions from other Phase III trials.

Advantages and Disadvantages

The distinct advantages of Tafenoquine are:

1. Activity against blood and liver stage parasites
2. Additional gametocidal and sporontocidal activity.
3. Long half life
4. Potential drug of choice for travelers to endemic areas for short periods
5. Better compliance
6. Can be stopped immediately upon leaving endemic area
7. Chemoprophylactic properties against both P. falciparum and P. vivax
8. Has potential for radical cure of P. vivax

Disadvantages associated with it are:

1. Safety in pregnancy has not yet been determined
2. There is a risk of hemolysis in G6PD deficiency

CONCLUSION

Tafenoquine is a long-acting analogue of primaquine. For non- immune travelers traveling to endemic areas for few weeks, tafenoquine, has the potential to be the drug of choice. Besides, on leaving the endemic region, tafenoquine need not be continued as it has an extended half-life and

potential transmission blocking properties and hence there are minimum chances of treatment failure due to non-compliance. Tafenoquine, besides chemoprophylaxis, also has the potential for radical cure of vivax malaria. Tafenoquine may also have a role in post exposure or terminal prophylaxis in travelers, in order to eliminate the hypnozoite stages of vivax malaria upon leaving an endemic area. However, prior to its administration, G6PD deficiency and/or pregnancy need to be ruled out.

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