Atovaquone/Proguanil : A New Drug Combination to Combat Malaria

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Introduction

Emerging drug resistance and intolerance to standard agents such as chloroquine, sulfadoxine/pyrimethamine and mefloquine has highlighted the need for new antimalarials. Although chloroquine remains the treatment of choice, a fixed dose combination of atovaquone/proguanil may be considered as the most promising alternative for prevention and treatment of malaria in chloroquine resistant areas. The combination has been found to be highly effective with a good tolerance and safety profile [1].

Mode of Action

Atovaquone, an analogue of coenzyme Q (Ubiquinone), acts on the plasmodium cytochrome B, where it interrupts electron transport and causes loss of mitochondrial membrane potential [2]. Proguanil exerts its effect by means of the metabolite cycloguanil, a dihydrofolate reductase inhibitor. It also accelerates the loss of mitochondrial membrane potential.

Atovaquone/proguanil acts synergistically against the malarial parasite and avoids the rapid selection of atovaquone resistant parasites whenever the parasites are exposed to the action of atovaquone alone. This combination also brings about enzymatic inhibition of pyrimidine synthesis.

Formulation and Dosage

Atovaquone/proguanil combination is available as Malarone and is marketed by GlaxoSmithKline. Malarone is a fixed dose combination of 250 mg atovaquone and 100 mg proguanil hydrochloride per adult strength tablet. The adult dosage is four tablets each day for three days. Besides, malarone is also available as paediatric tablets containing 62.5 mg of atovaquone and 25 mg of proguanil. The dosage is two paediatric

tablets each day for children weighing 5-8 kg, three paediatric tablets for those weighing 9-10 kg, one adult strength tablet for those weighing 11-20 kg, two adult strength tablets for those weighing 21-30 kg, three adult strength tablets for those weighing 31-40 kg and four adult strength tablets for those weighing more than 40 kg, each day for three days.

Prophylactic treatment with malarone should be one adult strength tablet each day, started two days before entering a malaria-endemic area, continued daily during the stay and thereafter for seven days after returning from the endemic area. The dosage for prevention of malaria in the paediatric age group is one paediatric tablet for children weighing 11-20 kg, two paediatric tablets for those weighing 21-30 kg, three paediatric tablets for those weighing 31-40 kg and one adult strength tablet for those weighing more than 40 kg each day.

Efficacy

Atovaquone/proguanil, when evaluated in clinical trials for treatment of uncomplicated malaria, led to a higher (87-100% versus 72-88%) or equally effective (94-100% versus 90-100%) cure rate than the other antimalarials. When evaluated in prophylactic clinical trials, the success rates in the atovaquone/proguanil and placebo groups ranged from 98-100% and 48-82%, respectively [3]. Atovaquone/proguanil has effectively treated *P. vivax* malaria in South East Asia, where prevalence rates of chloroquine resistant cases are high. Various studies have demonstrated an efficacy of more than 95%. The combination has also reported cure rates of 94 - 100% for *P. falciparum* infections in South East Asia and Africa. However, few cases of treatment failure have been reported from sub-Saharan Africa, with some of the isolates having genetically confirmed markers of resistance, i.e. mutations in the cytochrome B gene [4].

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Though highly effective in treating *P falciparum* and *P vivax* malaria, atovaquone/proguanil has poor outcome in *P vivax* malaria when used alone. The drug combination has no effect on hypnozoites of *P vivax*, thus leading to high relapse rates (>75%). However, if primaquine is given daily for 14 days following completion of atovaquone/proguanil therapy in *P vivax* malaria, most patients remain free of parasitemia during the follow-up period.

The usefulness of atovaquone/proguanil has also been demonstrated in multi-drug resistant malaria. In a study conducted in Thailand, 97.8% of the 140 multi-drug resistant *P falciparum* cases responded to therapy and remained clear of parasitemia at follow-up [5]. Atovaquone/proguanil is highly effective for prophylaxis against malaria and is now recommended as a prophylactic alternative to mefloquine or doxycycline in chloroquine-resistant areas.

Adverse Effects

At the doses employed for the treatment of malaria, adverse reactions with atovaquone/proguanil have been mild. The common adverse effects are abdominal pain (17%), nausea (12%), vomiting (12%), headache (10%), diarrhoea (8%), asthenia (8%), pruritus (6%), anorexia (5%), and dizziness (5%). The rare adverse reactions include anaphylaxis, angioedema, phototoxicity, Stevens-Johnson syndrome, erythema multiforme, hallucinations, seizures and hepatitis. Atovaquone/proguanil is better tolerated than chloroquine or sulfadoxine/pyrimethamine. Although recent studies in pregnant women have shown the regimen to be well tolerated with no evidence of toxicity to the mother or foetus, further studies are needed before its safety during pregnancy can be fully established.

Emergence of Resistance

Recent studies have shown that resistance may emerge during therapy with atovaquone/proguanil. This suggests that the synergistic interaction between the two drugs is lost following mutations in the parasite cytochrome B. Several factors may contribute to emergence of resistance, including high parasite burdens, rapid metabolism of proguanil, exposure to suboptimal drug concentrations, or prior exposure to related drugs.

Conclusion

Atovaquone/proguanil may well become the first line drug combination in the treatment and prophylaxis of malaria, due to its excellent safety profile and the oral route of administration.

Conflicts of Interest

None identified

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ERRATUM

1. Update Article: Prostate Cancer –What's New? MJAFI 2008;64:51-6. In first line under paragraph Screening on page 54:-
For: The incidence of CaP in Asia and India (4.8-8 cases per lac population versus 140 per lac population) is more than ten times than that in USA and Europe.
Read: The incidence of CaP in Asia and India (4.8-8 cases per lac population versus 140 per lac population) is less than ten times than that in USA and Europe.
2. Case Report: A Case of Intramedullary Epidermoid Cyst. MJAFI 2008;64:72-3.
Title for : Intramedullary, Read: Intramedullary
For Authors: Lt Col MN Swamy, Read: Lt Col MN Swamy, Classified Specialist (Surgery & Neurosurgery), Brig PK Sahoo, Consultant (Surgery & Neurosurgery), Surg Cdr KI Mathai, Classified Specialist (Surgery & Neurosurgery), Lt Col GV Ramdas, Classified Specialist (Surgery & Neurosurgery), Lt Col K Prabhakaran, Classified Specialist (Anaesthesiology), Command Hospital (SC), Pune and Lt Col K Sahai, Classified Specialist (Pathology), Armed Forces Medical College, Pune.
3. Original Article : Cost-effectiveness Analysis For Technology Acquisition. MJAFI 2008;64: 46-9
In Table 2 on page 48, under Present Value Benefit in 1st year ; For : 13527408, Read : 0 and
under Present Value Cost For : Nil, Read : 1,35,27,408