Atovaquone

Class:
Atovaquone, 2-[trans-4-(4'-chlorophenyl) cyclohexyl]-3-hydroxy-1, 4-naphthoquinone, is a hydroxynaphthoquinone.

Antiparasitic Activity:
Atovaquone is active against asexual stages of *Plasmodium falciparum, Babesia spp., Pneumocystis carinii, Toxoplasma gondii, Cryptosporidium parvum, Septata intestinalis, Enterocytozoon hellem, Leishmania spp, Entamoeba histolytica/dispar* and *Trichomonas vaginalis.*

Mechanism of Action:
Atovaquone possesses a novel mode of action against *P. falciparum* through inhibition of the electron transport system at the level of cytochrome bc1 complex. Atovaquone also causes collapse of the parasite mitochondrial membrane potential in *P. falciparum*. The mechanism of action against *P. carinii* is unknown. The synergistic activity between proguanil and atovaquone (Figure 3) appears to be related to proguanil *per se*, and metabolism to cycloguanil is not required.

Mechanism of Resistance:
Atovaquone-resistant *P. falciparum* parasites contain point mutations in the cytochrome b gene.

Pharmacokinetics:
Atovaquone is a highly lipophilic compound with low aqueous solubility and limited oral bioavailability that varies with dose and diet. It is highly protein bound (>99.9%). The range of elimination half-lives in fasting healthy subjects given single oral doses of 225mg to 750mg was 70 to 84 hours (Table 1).

Dosage:
Treatment and prophylaxis of *Pneumocystis carinii* Pneumonitis.
The recommended dose is 1500mg daily, taken in two divided doses for 21 days for treatment and as a single dose of 1500mg for prevention taken with food.

Treatment and prophylaxis of *Plasmodium falciparum* Malaria.
A fixed dose combination tablet, containing atovaquone 250mg and proguanil hydrochloride 100mg, has been specifically developed (Malarone™; see below). For the treatment of adults, four tablets should be taken daily as a single dose at the same time each day for three consecutive days. Dosage for treatment of children is once daily as a single dose for three consecutive days and calculated according to body weight.

For prophylaxis in adults weighing over 40kg, one tablet should be taken daily commencing one or two days prior to travelling to an endemic area and continued daily for the duration of the stay and for seven days after leaving. Dosage for prophylaxis in children is calculated according to body weight.

Adverse Effects:
No serious or life-threatening adverse effects have been reported in individuals receiving atovaquone alone or in combination with proguanil (Table 3).

Pregnancy:
In the absence of adequate and well-controlled studies in pregnant women, atovaquone alone and in combination with proguanil should only be administered during pregnancy if the potential benefit outweighs the potential risk to the foetus.

Drug Interactions:
Reduction in plasma concentrations of atovaquone are seen when given in combination with rifampin, rifabutin and metaclopramide. Atovaquone increases the AUC of zidovudine through inhibition of Glucuronidation.

Brand names/Manufacturer:
Malarone™ (Atovaquone [250mg]; Proguanil hydrochloride [100mg]). A paediatric tablet is available containing atovaquone (62.5mg) and proguanil hydrochloride (25mg).
Mepron™ (Atovaquone; micro-particulate suspension containing 750mg/5ml).