MINIREVIEW

Antiparasitic Agent Atovaquone

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Atovaquone is a unique naphthoquinone with broad-spectrum antiprotozoal activity. It is effective for the treatment and prevention of *Pneumocystis carinii* pneumonia (PCP), it is effective in combination with proguanil for the treatment and prevention of malaria, and it is effective in combination with azithromycin for the treatment of babesiosis. There is also limited experience with other protozoans. It has found a role in the management of diseases such as malaria and PCP because drug resistance, intolerable side effects of medications, and variable efficacies have occurred with existing treatments. Although the antimicrobial actions of the naphthoquinones were demonstrated more than 50 years ago, clinical trials leading to Food and Drug Administration (FDA) approval of atovaquone have occurred largely over the last decade. This paper reviews the pharmacology and mechanism of action, clinical trials, and current uses of atovaquone.

PHARMACOKINETICS AND SIDE EFFECTS

Atovaquone (566C80), a hydroxy-1,4-naphthoquinone, is a structural analog of protozoan ubiquinone, a mitochondrial protein involved in electron transport. It is a highly lipophilic molecule with very low aqueous solubility. Currently, atovaquone is marketed as Mepron (GlaxoSmithKline), a yellow crystalline solid in a citrus-flavored liquid suspension (750 mg of atovaquone/5 ml of suspension) (product information, Mepron [atovaquone] suspension, 1999, GlaxoWellcome). When atovaquone was first released in 1992 it was as a tablet, but this formulation was discontinued because of poor and unreliable bioavailability (102). The drug was reformulated as a micronized suspension with small particle size that allowed improved absorption compared with that of the tablet. Atovaquone levels in blood are doubled when it is ingested with food containing significant fats and reach steady-state concentrations of 15 to 30 $\mu\text{g/ml}$ with doses of 750 to 1,500 mg (6, 29, 102; product information, Mepron [atovaquone] suspension, 1999, GlaxoWellcome).

Atovaquone is protein bound (>99%) but causes no significant displacement of other highly protein-bound drugs. However, concomitant administration of atovaquone with rifampin leads to a 40 to 50% reduction in atovaquone levels (product information, Mepron [atovaquone] suspension, 1999, GlaxoWellcome), and when it is given with tetracycline there is

a 40% reduction in levels (product information, Malarone [atovaquone and proguanil] tablets, 2000, GlaxoWellcome). (In vitro tetracycline exhibits synergy with atovaquone [16], and in small numbers of patients with *Plasmodium falciparum* malaria, atovaquone plus tetracycline was 100% curative [78].) There appears to be a lesser interaction with rifabutin (C. Gillotin, I. Grandpierre, and B. Sadler, abstr., Clinical Pharmacology and Therapeutics, 63:229, 1998). Atovaquone increases by about 33% the area under the concentration-time curve for zidovudine by inhibition of hepatic glucuronidation of zidovudine (73). The potential for increased toxicity of zidovudine in patients given both drugs should be considered by clinicians. Drug penetration into cerebrospinal fluid is minimal; atovaquone cerebrospinal fluid concentrations rarely exceed 1% of the plasma atovaquone concentration (101; product information, Mepron [atovaquone] suspension, 1999, GlaxoWellcome). There is no significant hepatic metabolism or renal elimination, and less than 1% of the drug is renally excreted. There is extensive enterohepatic cycling, with more than 94% of the drug eliminated in the feces over 3 weeks (101; product information, Mepron [atovaquone] suspension, 1999, GlaxoWellcome). At recommended doses, atovaquone has a long half-life, ranging from 51 to 77 h (29, 55, 101, 118). Infants and small children may handle atovaquone differently, requiring a dose adjustment (52).

Atovaquone is frequently used in combination with other agents. For treatment and prophylaxis of malaria it has been combined with the biguanide proguanil in a fixed combination. This drug is called Malarone (GlaxoSmithKline) and is available in an adult formulation (250 mg of atovaquone, 100 mg of proguanil) and a pediatric formulation (62.5 mg of atovaquone, 25 mg of proguanil). Although a detailed discussion of proguanil is beyond the scope of this paper, the following points should be made. Proguanil by itself has weak anti-*Plasmodium* activity, but following absorption and hepatic metabolism via the cytochrome P450 3A and 2C subfamilies, it is converted to the active metabolite cycloguanil (98), which is an effective dihydrofolate reductase inhibitor. The bioavailability of proguanil approaches 60% following oral ingestion (134). Steady-state levels of proguanil after oral dosing of atovaquone-proguanil (A-P) are about 40 ng/ml, and the levels of cycloguanil are about 10 ng/ml (6, 8).

Proguanil is a highly protein-bound molecule that, like atovaquone, does not appear to significantly displace other drugs. It is concentrated in erythrocytes, with intracellular concentrations exceeding five times the concentration in plasma (134). Hepatic metabolism accounts for the major path of elimination of proguanil, and 40% of the drug is renally elim-

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inated (6). The half-life of proguanil in adults and children ranges from 12 to 21 h (6; product information, Malarone [atovaquone and proguanil] tablets, 2000, GlaxoWellcome). There is genetic polymorphism of the cytochrome systems responsible for the metabolism of proguanil to cycloguanil (46), but this does not appear to have clinical relevance (59). A randomized study showed no alterations in the pharmacokinetics of either atovaquone or proguanil when they were used in combination (58).

Atovaquone as a single agent has a relatively favorable side effect profile. The widest experience with atovaquone has been in comparison to other agents in trials of the treatment and prevention of PCP in AIDS patients. In those studies, atovaquone has generally had fewer side effects than trimethoprim-sulfamethoxazole (SXT) (53, 56), parenteral pentamidine (21, 32), or dapsone (33). The most frequently reported adverse effects include maculopapular rash, nausea and diarrhea, and headache in 10 to 35% of persons. In one trial the incidence of rash correlated with an increase in the plasma atovaquone concentration (56). Side effects may resolve with continued treatment (36). Elevation of liver enzyme levels has also been documented (36, 118). Atovaquone does not cause bone marrow suppression, and because it lacks antibacterial activity, it should not affect the gastrointestinal flora. Overdoses of atovaquone suspension in three patients did not result in permanent injury (T. W. Cheung, Letter, *AIDS* **13**:1984–1985, 1999).

The addition of proguanil to atovaquone does not substantially alter the side effect profile. When A-P is taken for chemoprophylaxis for malaria, gastrointestinal side effects and headache predominate (49, 74, 92, 114, 125). In studies of the treatment of malaria with higher doses of A-P, elevations of liver transaminase and bilirubin levels are recorded in approximately 15% of treated patients (77, 79). This was particularly seen in Thai patients, possibly reflecting the concomitant effects of high rates of hepatitis B virus carriage. In most patients this resolves over 28 days.

MECHANISM OF ACTION

Atovaquone has broad-spectrum activity against *Plasmodium* spp., *P. carinii*, *Babesia* spp., and *Toxoplasma gondii*. Its mechanism of action has been most completely elucidated for *Plasmodium* spp. The drug is structurally similar to the inner mitochondrial protein ubiquinone (also called coenzyme Q), which is an integral component of electron flow in aerobic respiration. Ubiquinone accepts electrons from dehydrogenase enzymes and passes them to electron transport cytochromes (126). The passage of electrons from ubiquinone to cytochrome *bc*₁ (complex III) requires binding of coenzyme Q-complex III at the Qo cytochrome domain; it is this step which is inhibited by atovaquone (39, 131). The structure of the Qo cytochrome binding site has been defined and explains the selective toxicity of atovaquone to parasitic mitochondria (120). The consequence of this inhibition is the collapse of the mitochondrial membrane potential (121). Several parasite enzymes are linked to the mitochondrial electron transport system and are inhibited. Included among these enzymes is dihydroorotate dehydrogenase (DHOD), which is required in the biosynthesis of pyrimidines. Because plasmodia are unable to scavenge pyrimidines for DNA synthesis and are required to

synthesize them de novo, inhibition of DHOD results in parasite death (43). ATP generation is another physiologic process linked to an intact mitochondrial membrane potential, although in plasmodia ATP levels are not consistently decreased by the administration of atovaquone. The effect of atovaquone on malaria parasites occurs at nanomolar concentrations (51).

When used as a single agent in patients with malaria, atovaquone is effective, but it is associated with unacceptable recrudescence rates and decreased parasite susceptibility following treatment (22, 78). Therefore, other drugs have been studied as synergistic partners. Proguanil demonstrated synergistic activity in vitro even against atovaquone-resistant *P. falciparum* isolates (16). The activity of proguanil when it was used with atovaquone was generally stronger than that of its metabolite cycloguanil, which was unexpected since the antimalarial effect of proguanil has been attributed to dihydrofolate reductase inhibition by cycloguanil (98). This independent effect of proguanil may be the result of its enhancement of atovaquone's collapse of the mitochondrial membrane potential (122). Therefore, proguanil may be synergistic with atovaquone by enhancement of the activity of atovaquone and through inhibition of dihydrofolate reductase by cycloguanil.

It is presumed that atovaquone kills other infectious agents through the same mechanism: inhibition of ubiquinone binding to cytochrome *b*. This has been demonstrated for *T. gondii* (84) and *P. carinii*, which has recently been reclassified from a parasite to a fungus (124). In *Pneumocystis*, inhibition of ubiquinone binding results in inhibition of DHOD (61) and markedly decreased levels of ATP (26). The effects of atovaquone on *Pneumocystis* occur at micromolar concentrations (24, 26).

Mutations of the cytochrome *b* gene have occurred in atovaquone-resistant isolates of *T. gondii* (84), *Plasmodium* spp. (120, 128, 129), and *Pneumocystis* (133). Resistance may be conferred by single amino acid substitutions, and study of these resistant isolates has been helpful in obtaining an understanding of the mechanism of action of atovaquone. Mutations in the cytochrome *b* gene may occur at higher rates since the gene is located in the mitochondrial genome, which is subject to less efficient proofreading than genes in the nuclear genome. The clinical significance of gene mutations has not been determined in *Pneumocystis* (67), but in malaria the concern about the development of resistance contributed to the addition of proguanil to atovaquone.

The use of atovaquone given with the macrolide azithromycin for the treatment of babesiosis has recently been studied. Atovaquone's antibabesial mechanism likely involves inhibition of mitochondrial electron transport, although elucidation of this requires further investigation.

REVIEW OF CLINICAL TRIALS

***P. carinii*.** Pneumonia caused by *P. carinii* is a common and potentially fatal opportunistic infection in immunocompromised patients. Prior to the use of highly active antiretroviral therapy, PCP affected nearly 75% of all AIDS patients at some point in their course (94). Even in the era of highly active antiretroviral therapy there remains a substantial morbidity and mortality from PCP in human immunodeficiency virus

TABLE 1. Atovaquone treatment of AIDS patients with PCP

Study, yr (reference)	Drug (dose ^a)	No. (%) of patients:				
		Enrolled	Evaluated	With treatment-limiting side effects	With failure of therapy	With successful outcome
Falloon et al., 1991 (36)	Atovaquone ^c at 750 mg t.i.d. for 5 d; b.i.d. for 16 days	10	10	0	1 (10)	9 (90)
	Atovaquone ^c at 750 mg t.i.d. for 21 days	15	15	0	2 (13)	13 (87)
	Atovaquone ^c at 750 mg q.i.d. for 21 days	9	7	2 (22)	2 (22)	5 (56)
Hughes et al., 1993 (53)	Atovaquone ^c at 750 mg t.i.d. for 21 days	160	138	11 (7)	28 (18)	99 (62)
	SXT at 1,600/320 mg for 21 days	162	146	33 (20)	10 (6)	103 (64)
Dohn et al., 1994 (32)	Atovaquone ^c at 750 mg t.i.d. for 21 days	56	50	2 (4)	16 (29)	32 (57)
	Pentamidine at 3-4mg/kg/day for 21 days	53	49	19 (36)	9 (17)	21 (40)

^a t.i.d., three times a day; b.i.d., two times a day; q.i.d., four times a day.

^b Percentage of originally enrolled patients taking initial treatment drug.

^c Tablet formulation of atovaquone.

(HIV)-infected persons (63). The drug of choice for the prophylaxis and treatment of PCP is SXT (19, 37, 69), which in numerous comparative trials has been demonstrated to have efficacy superior to that of other agents (13, 44, 53, 60, 108, 110). Despite its efficacy, many patients managed with SXT will experience treatment-limiting side effects such as rash, renal dysfunction, hepatitis, and bone marrow suppression (53, 60, 108). Therefore, alternative medications have been examined and may be necessary for some patients. The drugs most commonly used for primary and secondary prophylaxis are dapsone with or without pyrimethamine, aerosolized pentamidine, and atovaquone (19, 37, 69); and the drugs most commonly used for treatment are intravenous pentamidine, clindamycin plus primaquine, dapsone plus trimethoprim, and atovaquone (38).

Following demonstration of the effectiveness of atovaquone in a rat model of *Pneumocystis* infection (54), in 1991 a preliminary study with atovaquone was carried out with humans with PCP (36). Falloon et al. (36) showed that atovaquone given at a dose of 750 mg orally (in tablet form) two to four times daily for 21 days successfully treated 79% of 34 adult AIDS patients with mild to moderate PCP (defined as an arterial oxygen tension of ≥ 60 mm Hg) (Table 1). The drug was well tolerated by patients who took it two or three times daily. In November 1992, atovaquone received FDA approval for treatment of mild to moderate PCP in patients intolerant of SXT. Following approval, two randomized comparative studies were published which demonstrated efficacy (Table 1).

The first study was a double-blind, multicenter comparison of atovaquone to SXT in patients with mild to moderate PCP (with an alveolar-arterial oxygen gradient of ≤ 45 mm Hg) (53). Atovaquone was slightly less effective (a 20% failure rate with atovaquone versus a 7% failure rate with SXT [$P = 0.002$]) but was better tolerated (7% of the patients receiving atovaquone required a change in therapy, whereas 20% of the patients receiving SXT required a change in therapy [$P = 0.001$]). Overall rates of treatment success (classified as effective treatment plus no treatment-limiting adverse effects) for the SXT and the atovaquone cohorts were 64 and 62%, respectively. An important finding was that treatment success with atovaquone correlated with the levels of drug in blood. A level ≥ 15 $\mu\text{g/ml}$ correlated with therapeutic success in 98% (42 of 43) of per-

sons, whereas a level < 15 $\mu\text{g/ml}$ was associated with therapeutic success in 66% (46 of 70) of persons.

The second study was an open-label, randomized comparison of atovaquone with intravenous pentamidine in patients with mild to moderate PCP (32). Overall, the efficacy of atovaquone was similar to that of pentamidine. There were more patients who did not respond to treatment with atovaquone (29% for atovaquone versus 17% for pentamidine [$P = 0.18$]), but more patients on pentamidine had treatment-limiting side effects (36 versus 4% [$P < 0.001$]).

Two comparative trials that have examined atovaquone for prophylaxis of PCP have been published. The first study was an open-label, randomized trial in which daily atovaquone (1,500-mg suspension) was compared with daily dapsone (100 mg) in 1,057 patients intolerant of SXT (33). Each drug had similar failure rates (15.7 cases of PCP per 100 person-years for atovaquone and 18.4 cases of PCP per 100 person-years for dapsone). Overall, the drugs were similarly tolerated, although persons who were taking dapsone prior to randomization had more adverse events when they were placed on atovaquone than when they were left on dapsone (32.1 versus 8.4% [$P < 0.001$]). Persons newly assigned to the dapsone regimen had more side effects than those receiving atovaquone (58.4 versus 23.6% [$P < 0.001$]). Hypersensitivity reactions and anemia were more common with dapsone, and gastrointestinal symptoms were more common with atovaquone.

In the second study, atovaquone was compared with pentamidine in 549 SXT-intolerant HIV-infected patients (21). In the intention-to-treat analysis, once-daily atovaquone suspension (either 750 or 1,500 mg) had efficacy similar to that of monthly aerosolized pentamidine (300 mg) (PCP incidences, 25, 22, and 17%, respectively). Atovaquone was not as well tolerated, with treatment-limiting side effects occurring in 19% of the 750-mg group, 24% of the 1,500-mg group, and 8% of the pentamidine group. Rash, fever, and vomiting were most common in the atovaquone groups.

Although sequences for atovaquone resistance in the cytochrome *b* gene of *Pneumocystis* have been documented in isolates from persons who have failed prophylaxis (133) and in persons who have previously taken atovaquone (67), it has not

been determined whether these sequences account for the ineffectiveness of the drug in these persons.

Malaria. It is estimated that 300 million to 500 million of the world's population are infected with malaria and that approximately 2 million persons will die of the disease each year (140). For travelers to areas of endemicity, malaria presents a serious threat. In the United States, 1,000 to 1,500 cases of malaria are reported annually in persons who have visited areas where malaria is endemic (83). The development of widespread resistance of *P. falciparum* to chloroquine, which began in the 1960s in Asia and South America and which spread to Africa in the 1980s (119), led to the study and release of other chemoprophylactic agents.

Fansidar, a fixed combination of sulfadoxine and pyrimethamine, was one of the first agents recommended for prophylaxis; however, the risk of severe adverse cutaneous reactions secondary to sulfadoxine (87) has limited use of the drug to treatment of malaria (20, 85, 139). The addition of daily proguanil to weekly chloroquine has been recommended in areas with low rates of transmission of resistant parasites, such as South America and India (14, 139). Increasingly, however, use of this combination is not effective (76, 123), is difficult for the traveler to comply with (48), and for U.S. travelers, requires them to acquire proguanil overseas since it is not available in the United States. The Centers for Disease Control and Prevention no longer recommends use of this combination (20).

Mefloquine became the drug of choice when it was introduced in the early 1990s (75, 109) because it was found to be highly effective against both chloroquine-sensitive and chloroquine-resistant *P. falciparum* isolates (90, 123). Although it is still a first-line agent in chemoprophylaxis (20, 25, 139), concern about neuropsychiatric side effects led both health care providers and travelers to be cautious in using it. At prophylactic doses, mild neuropsychiatric effects of sleep disturbance, vivid dreams, and mood changes occur in 5 to 30% of persons (5, 48, 76, 95, 123) and severe reactions of psychosis or convulsions occur in 1 in 10,000 individuals or less (7, 123, 135). The drug should not be used in persons with a history of a seizure disorder, neuropsychiatric disorders, or cardiac conduction disturbances (20).

Doxycycline is an alternative that is effective for both chloroquine-resistant and mefloquine-resistant malaria, as may be found in forested border areas of Thailand with Myanmar (formerly Burma) and Cambodia (2, 90). It should not be taken by children aged 8 and younger or by pregnant women, it may predispose women to vaginal yeast infections, and it can cause gastrointestinal upset and photosensitivity reactions (20). The need for daily dosing for 4 weeks after one returns from an area where malaria is endemic may result in lower efficacy because of decreased compliance (89). Other alternative regimens are not as frequently used (64).

The potential problems with the existing antimalarials led to the study of atovaquone. When used as a single agent in the treatment of *P. falciparum* infection, atovaquone was highly effective, but it was associated with unacceptably high relapse rates (22, 77, 78), which prevented it from being marketed alone. As discussed earlier, *in vitro* studies demonstrated that proguanil was synergistic with atovaquone (16, 98), and in clinical studies, the addition of proguanil enhanced efficacy and

prevented the development of resistance (77, 78). Thus, proguanil was chosen as the partner for use with atovaquone.

Atovaquone was also effective as a single agent in prevention of falciparum malaria in a mosquito challenge study (115). In that randomized, double-blind, placebo-controlled study, subjects were infected with *P. falciparum* and given low-dose atovaquone (250 mg administered once 1 day prior to infection, six subjects), high-dose atovaquone (750 mg daily for 7 days beginning 1 day prior to infection, six subjects), or placebo (four subjects). Both of the atovaquone groups were 100% protected; all placebo-treated subjects developed malaria.

Importantly, that study determined that atovaquone had tissue schizonticidal activity, meaning that it killed parasites during the preerythrocytic (hepatic) stage of infection: a single 250-mg dose given before challenge was sufficient to prevent infection. This property of killing developing hepatic-stage parasites, known as causal prophylactic efficacy (23), allows discontinuation of atovaquone soon after leaving the area where malaria is endemic. The causal prophylactic activity of the combination agent A-P has also been demonstrated (8).

Trials of A-P with larger enrollments followed. Most of the trials of treatment and prophylaxis were conducted in residents of countries where malaria is endemic who had uncomplicated malaria and who were likely to be semi-immune to infection. Studies of treatment of *P. falciparum* malaria have been summarized by Looareesuwan et al. (77) and Kremsner et al. (72) and in Table 2. In randomized, controlled, open-label studies, A-P was more effective than mefloquine in adults in Thailand (79), was more effective than amodiaquine in adolescents and adults in Gabon (100), and was more effective than chloroquine alone or chloroquine plus sulfadoxine-pyrimethamine (Fansidar) in adolescents and adults in the Philippines (15). It demonstrated efficacy equivalent to those of quinine and tetracycline in adults in Brazil (28) and to that of sulfadoxine-pyrimethamine (Fansidar) in adolescents and adults in Zambia (88). A-P was as effective as halofantrine in an open trial conducted with children in Kenya (1), and it was also highly effective in a noncomparative trial with Thai children (107). In an open-label treatment study of nonimmune returned travelers with falciparum malaria, A-P was as effective as halofantrine (12). Finally, A-P was effective treatment for multidrug-resistant malaria, which may occur in some regions of Thailand (9, 107).

There are fewer studies concerning the efficacy of A-P in the treatment of non-falciparum malaria. It was effective treatment for *Plasmodium vivax* and *Plasmodium ovale* infections in 7 patients in Gabon (99) and for *P. vivax* infections in 35 patients in Thailand (80). The drug will not eradicate the hypnozoite phase of *P. vivax* or *P. ovale*, so treatment with primaquine phosphate is necessary to prevent relapses of these species.

Studies of the use of A-P for prophylaxis have been summarized by Shanks et al. (114) and in Table 3. In randomized, placebo-controlled trials, A-P demonstrated >95% protective efficacy in semi-immune adults in Kenya (113) and Zambia (125) and in children in Gabon (74).

Although A-P has shown excellent protection in semi-immune populations, there was concern that studies had not been carried out with nonimmune persons. Hogg et al. (49) recently published a comparison of A-P with chloroquine-proguanil in a multicenter study of 1,083 nonimmune travelers visiting re-

TABLE 2. Treatment of *P. falciparum* malaria with A-P

Study, yr (reference)	Country or group	Therapy (dose) ^a	No. (%) ^b of patients:		
			Enrolled	Evaluated	Cured
Looareesuwan et al., 1996 (78)	Thailand	A-P (1,000/400 mg) for 3 days	24	24	24 (100)
Radloff et al., 1996 (100)	Gabon	A-P (1,000/400 mg) for 3 days	71	63	62 (87 ^c)
		Amodiaquine at 600 g, 600 g, 300 mg	71	63	51 (72 ^c)
de Alencar et al., 1997 (28)	Brazil	A-P (1,000 g/400 mg) for 3 days	NS ^c	77	76 (99)
		Quinine (600 mg) t.i.d. for 7 days + tetracycline (250 mg) q.i.d. for 7 days	NS	77	77 (100)
Sabchareon et al., 1998 (107)	Thailand	A-P (by wt) for 3 days	32	26	26 (100)
Looareesuwan et al., 1999 (79)	Thailand	A-P (1,000 g/400 mg) for 3 days	91	79	79 (100)
		Mefloquine at 750 mg once and then at 500 mg after 6 h	91	79	68 (86)
Mulenga et al., 1999 (88)	Zambia	A-P (1,000 g/400 mg) for 3 days	82	80	80 (100)
		Pyrimethamine (75 mg) + sulfadoxine (1,500 mg) once	81	80	79 (100)
Anabwani et al., 1999 (1)	Kenya ^d	A-P (by wt) for 3 days	84	81	76 (94)
		Halofantrine (8 mg/kg) every 6 h for three doses	84	83	75 (90)
Bustos et al., 1999 (15)	Philippines	A-P (by wt) for 3 days	55	54	54 (100)
		Chloroquine at 600 mg once and then at 300 mg once at 6, 24, and 48 h	23	23	7 (30)
		Chloroquine + pyrimethamine (75 mg) + sulfadoxine (1,500 mg) once	32	32	28 (88)
Bouchard et al., 2000 (12)	Nonimmune travelers	A-P (1,000 g/400 mg) for 3 days	25	21	21 (100)
		Halofantrine (500 mg) every 6 h for three doses	23	20	20 (100)

^a t.i.d., three times a day; q.i.d., four times a day.^b Percentage of evaluated patients^c NS, not stated.^d Pediatric population.^e Percentage of enrolled patients.

gions of the world where malaria is endemic. Although the primary end point was the frequency of adverse events and not protective efficacy and there was no placebo group, so the incidence of malaria could not be determined (the presence of anti-*P. falciparum* sporozoite antibodies was used as a surrogate marker of infection), only one case of *P. ovale* malaria was documented in the A-P group 28 days following the return from travel. This case was consistent with relapsed malaria from hypnozoite forms of the parasite. With no cases of *P. falciparum* in the A-P group and three cases in the chloroquine-proguanil group, there was an estimated minimum protective efficacy of A-P against *P. falciparum* of 100% (95% confidence interval, 59 to 100%).

A second study, by Overbosch et al. (92), with a design similar to that of the study of Hogh et al. (49) compared A-P with mefloquine in 1,013 nonimmune travelers. A-P was well tolerated, with fewer neuropsychiatric side effects (14 versus 29% [$P = 0.001$]), similar gastrointestinal side effects (16 versus 19% [$P =$ not significant]), and fewer treatment-limiting side effects (1 versus 5% [$P = 0.001$]). No cases of malaria were seen in either treatment group. Further support for prophylactic efficacy in nonimmune individuals comes from a small trial conducted with South African workers traveling to areas where malaria is endemic (132) and an unpublished study with pediatric travelers [D. Camus, D., D. Malvy, H. Schilthuis, B. Hogh, D. Hamilton, N. S. Roskell, G. B. Miller, and the Malarone International Study Team, Abstract, Am. J. Trop. Med. Hyg. 65(Suppl.):344–345, 2001]. A randomized, placebo-con-

trolled protective efficacy trial of A-P in nonimmune transmitters in Indonesia demonstrated that it had 81% protective efficacy against *P. vivax* (K. Baird, M. Lacy, P. Sismadi, R. Gramzinski, M. Bangs, H. Basri, J. Maguire, J. Ling, M. Sabandar, I. Krisin Wiady, M. Barcus, J. Scott, D. Fryauff, S. Hoffman, and G. Miller, Abstr. Annu. Meet. Am. Soc. Trop. Med. Hyg., 2000).

Babesiosis. Babesiosis, caused by the intraerythrocytic parasites of the genus *Babesia*, is an emerging infectious disease of persons living in coastal New England states and New York State, parts of the upper Midwest, and to a lesser extent, the West Coast (50). Most cases in the United States are caused by the rodent parasite *Babesia microti* and are transmitted by ticks of the *Ixodes* genus. In Europe, the few reported cases are usually caused by the bovine parasite *Babesia divergens*. Illness includes asymptomatic infection (71, 106), a self-limited flulike illness (41), and a severe life-threatening infection which resembles malaria. Severe illness is associated with advancing age; immunosuppression, including that caused by HIV infection and AIDS; or the absence of a spleen (35, 45, 86, 104).

In the early 1980s many traditional antiparasitic agents were evaluated for their therapeutic efficacies against babesiosis; however, only the combination of quinine and clindamycin was found to be adequately effective (18, 105, 138). In patients with life-threatening *Babesia* infections and high levels of parasitemia, red blood cell exchange transfusions may also be necessary (34, 62). Because of the frequent toxicity associated with quinine therapy (tinnitus, vertigo, and gastrointestinal upset)

TABLE 3. Prophylaxis of *P. falciparum* malaria with A-P

Study, yr (reference)	Country or group	Therapy (dose)	No. (%) of patients:			% protective efficacy (95% CI) ^b
			Enrolled	Evaluated	With cases of <i>P. falciparum</i> Malaria	
Shanks et al., 1998 (113)	Kenya	A-P (250/100 mg) q.d. ^d	70	54	0	100 (70–100)
		A-P (500/200 mg) q.d.	67	54	0	100 (70–100)
		Placebo	68	54	28 (52)	
Lell et al., 1998 (74)	Gabon ^c	A-P (dose by wt) q.d.	160	115	0	100 (83–100)
		Placebo	160	137	25 (18)	
Sukwa et al., 1999 (125)	Zambia	A-P (250/100 mg) q.d.	136	102	2 (2)	95 (79–100)
		Placebo	138	111	41 (37)	
Hogh et al., 2000 (49)	Nonimmune travelers	A-P (250/100 mg) q.d.	540	501	0	100 (59–100) ^e
		Chloroquine (500 mg salt) weekly + proguanil (100 mg) q.d.	543	507	3 (1)	70 (35–93) ^e
Overbosch et al., 2001 (92)	Nonimmune travelers	A-P (250 mg/100 mg) q.d.	508	489	0	100 (48–100) ^e
		Mefloquine (250 mg) weekly	505	477	0	100 (48–100) ^e
van der Berg et al., 1999 (132)	South Africa (nonimmune individuals)	A-P (250/100 mg) q.d.	175	113	1 (<1)	

^a Percentage of evaluated patients.^b CI, confidence interval.^c Pediatric population.^d q.d., once a day.^e The estimated minimum protective efficacy based on the number of documented cases plus the number of cases identified by a surrogate marker (the presence of circumsporozoite antibody).

(71) and some cases of treatment failure (47), atovaquone alone and atovaquone in combination with other drugs have been evaluated as treatments.

Initial studies conducted with hamsters infected with *B. microti* found that atovaquone was more effective than quinine plus clindamycin, even in steroid-treated animals (57). Atovaquone's effectiveness was further documented in gerbils infected with *B. microti* (42) or *B. divergens* (97) and in another study with hamsters (137). Because single-agent therapy did not result in complete eradication of the parasites, other agents were added for synergy. Azithromycin had shown efficacy alone and in combination with quinine for the treatment of *B. microti* infections in hamsters (136). When azithromycin was added to atovaquone in studies with hamsters, it prevented the recrudescence parasitemia that occurred when atovaquone was used alone (137). Two case reports demonstrating the efficacy of azithromycin and quinine in human babesiosis (112, 116) further supported a role for azithromycin. Therefore, the combination of azithromycin plus atovaquone seemed justified on the basis of its efficacy and excellent patient tolerance of each of the agents.

Limited clinical experience with atovaquone plus azithromycin was reported as part of case reports (11, 31) until Krause et al. (70) published a description of their experience with the combination compared with clindamycin plus quinine in 58 subjects with non-life-threatening *Babesia* infections. In their randomized, open-label, prospective trial, atovaquone (750 mg twice daily) plus azithromycin (500 mg once and then at 250 mg daily) was comparable to clindamycin (600 mg every 8 h) and quinine (650 mg every 8 h); both courses were given for 7 days. Fever resolved by 8 days in those receiving atovaquone plus azithromycin and by 7 days in those receiving clindamycin plus quinine. All symptoms attributed to babesiosis resolved by 3

months in 65% of those receiving atovaquone plus azithromycin and in 73% of those receiving quinine plus clindamycin; by 6 months no patient had symptoms. Every patient had clearance of *Babesia* DNA by 12 weeks. There were significant differences in side effects. Seventy-two percent of those receiving quinine and clindamycin had symptoms attributed to the drugs (diarrhea, tinnitus, or decreased hearing ability were the most common), whereas 15% of those receiving atovaquone plus azithromycin experienced side effects (usually diarrhea or rash). Weiss et al. (L. M. Weiss, M. Wittner, and H. B. Tanowitz, Letter, N. Engl. J. Med. 344:773, 2001) have also reported successful therapy with higher initial doses of azithromycin (600 mg daily).

Other parasites. There is limited information concerning the efficacy of atovaquone against other parasitic infections. For toxoplasmosis, most clinical experience with atovaquone has been with HIV-infected or AIDS patients. In this group, *T. gondii* is usually a reactivation infection of the central nervous system (CNS) in persons who have advanced immunosuppression (82). CNS toxoplasmosis still affects 7% of AIDS patients (63). Although pyrimethamine plus sulfadiazine or clindamycin are the drugs of choice for therapy and secondary prophylaxis of toxoplasmosis (19, 27, 69, 81, 82), some patients are intolerant of one of these regimens and require alternative therapies.

Atovaquone at nanogram-per-milliliter concentrations has been shown to have a high level of activity against tachyzoites in in vitro cell culture (3, 103), but higher concentrations of atovaquone were required to kill bradyzoites within cysts (3). In murine models of toxoplasmosis, atovaquone was also effective (51), but efficacy was enhanced when other agents were added to atovaquone, such as pyrimethamine or sulfadiazine (4), clindamycin (30), or clarithromycin (103). An experimen-

tal intravenous preparation was highly effective in a mouse model of reactivated toxoplasmosis (111).

Several small, noncomparative trials used atovaquone in the tablet form as salvage therapy for CNS disease in AIDS patients who were intolerant of or who failed standard regimens (68, 118). Forty to 80% of these patients had a complete or partial response to treatment. The largest clinical experience was a multicenter trial of atovaquone (750 mg in tablet form every 6 h for 6 weeks) in 93 persons who were intolerant of pyrimethamine plus sulfadiazine or clindamycin or who were failing therapy (130). At 6 weeks, 37% of patients had a complete or partial response as determined radiologically and 52% had a complete or partial response as determined clinically. There was a positive correlation of clinical outcome with atovaquone levels, which was a finding similar to that from trials of atovaquone for the treatment of PCP, in which higher levels of the drug in blood were associated with improved outcomes (53).

There is one trial of atovaquone use in immunocompetent patients with ocular toxoplasmosis (93). In these persons, the tablet form (750 mg four times daily) was given with prednisone as needed to control intraocular inflammation. There was improvement or stabilization of infection in the 17 patients treated.

Use of SXT or dapsone plus pyrimethamine as prophylaxis against PCP will also provide primary prophylaxis against toxoplasmosis (17, 40, 91, 96). If preventive therapy is tolerated, both regimens are more effective in preventing toxoplasmosis than pentamidine, which by itself will not prevent the disease (13). There are only limited data on the use of atovaquone as primary prophylaxis against toxoplasmosis. When the suspension formulation of atovaquone was compared to dapsone alone for the prevention of PCP, there was no difference in the number of cases of toxoplasmosis (33). Overall, 4% of patients seropositive for *Toxoplasma* developed toxoplasmosis. When atovaquone was used as secondary prophylaxis in patients intolerant of SXT or dapsone, 26% of persons relapsed with disease (66). This is similar to the results obtained for standard secondary prophylaxis with pyrimethamine plus sulfadiazine or clindamycin (65).

When atovaquone was used in suspension form for the treatment of human visceral leishmaniasis, it demonstrated only partial activity either as a single agent or when combined with fluconazole (127).

CONCLUSIONS

Atovaquone is a novel naphthoquinone with several clinical applications. The current clinical uses and dosing recommendations (adult doses; the full recommendations of the manufacturer should be consulted) for atovaquone are as follows: for prophylaxis against PCP, 1,500 mg once daily with meals; for treatment of mild to moderate PCP (defined as an arterial oxygen tension of ≥ 60 mm Hg or an alveolar-arterial oxygen gradient of ≤ 45 mm Hg), 750 mg twice daily with meals for 21 days; for prophylaxis against malaria, A-P (250/100-mg tablet) daily taken with food or a milky drink beginning 1 to 2 days before exposure and continuing for 7 days after the individual has left the area where malaria is endemic; for treatment of malaria, A-P (four 250/100-mg tablets) daily for 3 days (the

FDA indication is for treatment and prophylaxis of *P. falciparum* malaria; however, evidence indicates that atovaquone has activity against non-*P. falciparum* species [see above]; primaquine phosphate is required for radical cure of *P. vivax* or *P. ovale* infection); and for babesiosis, atovaquone at 750 mg twice daily plus azithromycin at 500 mg once and then at 250 mg once daily for 7 to 10 days. Babesiosis is not an FDA-approved indication for atovaquone. Some experts give azithromycin at 1 g daily for 3 days and then 500 mg daily (85); in some hosts, e.g., immunocompromised individuals, therapy may need to be prolonged beyond 7 to 10 days.

Atovaquone is an effective alternative to SXT for the treatment of PCP, particularly when adequate levels in blood can be obtained. The currently available suspension form (Mepron) is more reliable in this regard. It has treatment efficacy similar to that of pentamidine and carries fewer side effects. Because atovaquone has not been studied in severely ill persons with PCP, it should be limited to those with mild to moderate illness (an alveolar-arterial oxygen gradient of ≤ 45 mm Hg or an arterial oxygen tension of ≥ 60 mm Hg).

Atovaquone is an alternative to SXT for prophylaxis for PCP. Although it may not be as effective as dapsone for prophylaxis, it is better tolerated, which leads to similar overall success rates. It has efficacy similar to that of aerosolized pentamidine administered monthly.

The combination medication A-P (Malarone) will find an important place in both the prevention and the treatment of *P. falciparum* malaria. It is ideal for persons with short-term exposure to malaria parasites, since it can be started on the day before exposure and needs to be continued for only 7 days following exposure because of its causal prophylactic effect. This short duration of use following travel should contribute to increased rates of compliance with medication recommendations since many persons discontinue chemoprophylaxis for malaria after leaving the area where malaria is endemic. A-P also provides an alternative to doxycycline for persons traveling to areas with multidrug-resistant *P. falciparum* isolates. The availability of pediatric tablets makes dosing easier for children, since pediatric formulations of the agents currently available in the United States are not provided. It can also be carried for self-treatment of presumptive malaria in travelers receiving other prophylactic medications.

The efficacy of atovaquone plus azithromycin in the treatment of babesiosis may move this combination ahead of the standard treatment of quinine plus clindamycin in those who do not need parenteral therapy and who are generally not as severely ill. Further experience with all types of patients would be welcome.

The role of atovaquone in the treatment and prophylaxis of CNS toxoplasmosis in AIDS patients is not well defined. It can be used as salvage therapy in SXT-intolerant patients and is likely to provide some protection against toxoplasmosis when it is taken for primary prophylaxis against PCP. Some experts would add pyrimethamine when using atovaquone for the treatment or prevention of toxoplasmosis (19, 85). More studies are required before firm recommendations can be given.

The advantages of atovaquone include oral dosing, few treatment-limiting side effects, and an excellent safety profile. A disadvantage is its bioavailability. Although this has been improved with the suspension formulation, in persons with

decreased intestinal absorption the effectiveness of atovaquone may be decreased, particularly during management of AIDS patients who have PCP or toxoplasmosis.

High cost is another disadvantage. Atovaquone is 50- to 100-fold more expensive than dapsone or SXT (H. W. Horowitz and G. P. Wormser, Letter, *N. Engl. J. Med.* **340**:1512–1513, 1999). This further adds to the already high cost of management of HIV infection. When considering the use of A-P for the prevention of malaria, costs will be similar to those for mefloquine for trips of 2 weeks or less (92), but it will be far more expensive than doxycycline. For malaria prevention by persons living in the developing world, cost would likely be prohibitive unless the drug is donated; and then issues of access, sustainability, and resistance need to be considered (10, 117; F. Nosten, Editorial, *Lancet* **356**:1864–1865, 2000)).

Finally, the implications of developing resistance to atovaquone are not yet understood for *Pneumocystis* or *Toxoplasma* but will require further testing and evaluation. With malaria, it is hoped that the judicious use of the drug and its combination with proguanil will decrease the development of resistance. This also will need to be closely monitored.

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