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NLM Citation: LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Atovaquone. [Updated 2017 Feb 2].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/

Atovaquone

Updated: February 2, 2017.

OVERVIEW

Introduction

Atovaquone is a naphthoquinone used for the prevention and treatment of Pneumocystis jevorici (formerly carinii) pneumonia and, in combination with proguanil, prevention and treatment of P. falciparum malaria. Atovaquone therapy is associated with low rates of serum enzyme elevations and has been linked to only rare cases of clinically apparent liver injury.

Background

Atovaquone (a toe' va kwone) is a synthetic naphthoquinone that acts by interfering with mitochondrial electron transport in susceptible organisms. Atovaquone is effective against chloroquine resistant P. falciparum, but is associated with a high rate of resistance, for which reason it is usually given in combination with other agents, most typically with proguanil. Atovaquone was approved for use in the United States in 1992 and the combination with proguanil in 2000. Current indications include treatment and prevention of Pneumocystis jiroveci (formerly carinii) pneumonia (atovaquone alone) and treatment and prevention of falciparum malaria (combined with proguanil). It is sometimes used off-label as a second line agent for Toxoplasma gondii. Atovaquone is available in tablets of 250 and 500 mg and as a suspension of 750 mg/5 mL under the brand name Mepron. A fixed combination of 250 mg of atovaquone and 100 mg of proguanil is available generically and under the brand name Malarone, which is used in a 3 day regimen (4 tablets daily) to treat drug resistant P. falciparum malaria and for the period of exposure (1 tablet daily) to prevent chloroquine resistant Plasmodium falciparium and vivax malaria. A pediatric formulation is also available. The recommended dosage of atovaquone varies by different indications. Specific recommendations on the use of atovaquone for management of opportunistic infections among persons with HIV infection are available at: http://aidsinfo.nih.gov/guidelines/, and recommendations on treatment and prevention of malaria on the CDC website at: http://www.cdc.gov/malaria/. Common side effects of atovaquone include headache, fever, anxiety, insomnia, vivid dreams, nausea, diarrhea, skin rash and itching.

Hepatotoxicity

Atovaquone has been linked to serum aminotransferase elevations in a small proportion of patients (1% to 6%). There have also been rare reports of clinically apparent, acute liver injury due to atovaquone. In one published case report (Case 1), the onset of injury was 25 days after starting (and a few days after stopping) treatment. The pattern of serum enzyme elevations was cholestatic. Immunoallergic manifestations (fever, rash and eosinophilia) were not prominent and autoantibodies were not present. The liver injury resolved within 2 months of stopping the medication. Because a combination of proguanil and atovaquone was used, either agent

could have been responsible for the injury. Atovaquone has also been linked to rare instances of Stevens Johnson syndrome, which is frequently accompanied by mild liver injury or liver enzyme elevations.

Likelihood score: D (possible rare cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which atovaquone might cause liver injury is unknown. Atovaquone is minimally metabolized by the liver, while proguanil is metabolized by the cytochrome P450 system (CYP 2C19). Either a toxic or an immunogenic metabolite may be responsible for the injury.

Outcome and Management

The severity of hepatic injury due to atovaquone varies from mild serum enzyme elevations that are asymptomatic and transient, to clinically apparent liver injury with jaundice. Acute liver failure, chronic hepatitis and vanishing bile duct syndrome have not been reported after atovaquone therapy. There does not seem to be cross reactivity to hepatic injury among the various antimalarial agents and switching to other drug can be safely done.

Drug Class: Antimalarial Agents, see also Proguanil

CASE REPORT

Case 1. Cholestatic hepatitis after course of atovaquone/proguanil for malaria prophylaxis.

[Modified from: Grieshaber M, Lämmli J, Marcus L. Acute hepatitis and atovaquone/proguanil. J Travel Med 2005; 12: 289-90. PubMed Citation]

A 31 year old man developed jaundice and abdominal pain a few days after a 25 day course of atovaquone (250 mg) and proguanil (100 mg) for malaria prophylaxis during travel. Other symptoms included poor appetite, itching, fatigue and dark urine. He had no previous history of liver disease or exposures to hepatitis and did not abuse alcohol. On examination, he had mild fever (37.5 ^{o}C) and was jaundiced. There was no mention of rash or eosinophilia. Serum bilirubin was mildly elevated at 2.9 mg/dL, and both ALT and alkaline phosphatase levels were prominently increased (Table). Tests for viral hepatitis A, B, C and E were negative as were autoantibody markers. MRI of the abdomen showed a normal appearing liver and biliary system. A liver biopsy was not done. His symptoms gradually improved and serum enzyme abnormalities eventually resolved approximately 8 weeks after initial presentation.

Key Points

Medication:	Atovaquone and proguanil
Pattern:	Cholestatic (R=1.7)
Severity:	2+ (jaundice, hospitalization)
Latency:	25 days
Recovery:	8 weeks
Other medications:	None

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
4 weeks	1 weeks	320	445	2.9	LDH 610 U/L
	2 weeks	330	410	2.2	
	3 weeks	710	330	0.6	
7 weeks	4 weeks	310	240	0.5	
	5 weeks	280	190	0.5	
	6 weeks	75	115	0.5	
	7 weeks	60	110	0.5	
11 weeks	8 weeks	25	105	0.5	
Normal Values		**<40**	**<92**	**<1.2**	

* Estimated from Figure 1.

Comment

A mild case of cholestatic hepatitis typical of drug induced liver injury, and the only medications being used were atovaquone and proguanil, either of which may have been the cause. The somewhat delayed decline in serum enzymes is typical of cholestatic forms of drug induced liver injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Atovaquone – Mepron®

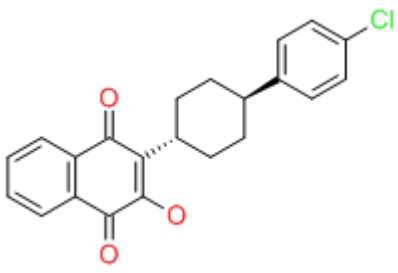
DRUG CLASS

Antimalarial Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Atovaquone	95233-18-4	C22-H19-Cl-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 02 February 2017

Zimmerman HJ. Antiprotozoal agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 623-5.

(Expert review of hepatotoxicity published in 1999; atovaquone is not discussed).

Vinetz JM, Clain J, Bounkeua V, Eastman RT, Fidock D. Chemotherapy of malaria. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1383-418.

(Textbook of pharmacology and therapeutics).

Høgh B, Clarke PD, Camus D, Nothdurft HD, Overbosch D, Günther M, Joubert I, et al.; Malarone International Study Team. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in non-immune travelers: a randomised, double-blind study. Malarone International Study Team. Lancet 2000; 356: 1888-94. PubMed PMID: 11130385.

(Controlled trial of atovaquone vs chloroquine combined with proguanil as malaria prophylaxis in 1008 travelers; efficacy was similar, but gastrointestinal upset was more common with chloroquine [20% vs 12%]; among 180 with laboratory testing "No clinically important laboratory abnormalities were identified").

Overbosch D, Schilthuis H, Bienzle U, Behrens RH, Kain KC, Clarke PD, Toovey S, et al. Malarone International Study Team. Atovaquone-proguanil versus mefloquine for malaria prophylaxis in nonimmune travelers: results from a randomized, double-blind study. Clin Infect Dis 2001; 33: 1015-21. PubMed PMID: 11528574.

(Controlled trial of atovaquone-proguanil vs mefloquine of malaria prophylaxis in 483 travelers; similar efficacy [100%], but neuropsychiatric side effects were more common with mefloquine [29% vs 14%] including insomnia, anxiety, vivid dreams, dizziness and trouble concentrating; no mention of liver injury and ALT levels were not monitored).

Camus D, Djossou F, Schilthuis HJ, Høgh B, Dutoit E, Malvy D, Roskell NS, et al.; International Malarone Study Team. Atovaquone-proguanil versus chloroquine-proguanil for malaria prophylaxis in nonimmune pediatric travelers: results of an international, randomized, open-label study. Clin Infect Dis 2004; 38: 1716-23. PubMed PMID: 15227617.

(Controlled trial of atovaquone vs chloroquine combined with proguanil as malaria prophylaxis in 221 children; efficacy was similar [100%], but side effects were slightly more frequent with chloroquine [mostly gastrointestinal]; no mention of liver injury or ALT elevations).

Taylor WR, White NJ. Antimalarial drug toxicity: a review. Drug Saf 2004; 27: 25-61. PubMed PMID: 14720085.

(Review of the toxicities and side effects of antimalarial agents; mentions that atovaquone/proguanil can cause minor ALT elevations, but clinically apparent hepatotoxicity is not mentioned).

Grieshaber M, Lämmli J, Marcus L. Acute hepatitis and atovaquone/proguanil. J Travel Med 2005; 12: 289-90. PubMed PMID: 16256055.

(31 year old man developed jaundice and abdominal pain 25 days after starting atovaquone/proguanil prophylaxis [bilirubin 2.9 mg/dL, ALT 320 U/L, Alk P 445 U/L], resolving slowly over next 8 weeks: Case 1).

Patel SN, Kain KC. Atovaquone/proguanil for the prophylaxis and treatment of malaria. Expert Rev Anti Infect Ther 2005; 3: 849-61. PubMed PMID: 16307498.

(Review of chemistry, clinical results and safety of atovaquone/proguanil; states that the combination is well tolerated, and ALT elevations are not mentioned).

Devarbhavi H, Dierkhising R, Kremers WK, Sandeep MS, Karanth D, Adarsh CK. Single-center experience with drug-induced liver injury from India: causes, outcome, prognosis, and predictors of mortality. Am J Gastroenterol 2010; 105: 2396-404. PubMed PMID: 20648003.

(313 cases of drug induced liver injury were seen over a 12 year period at a large hospital in Bangalore, India; none were attributed to antimalarials).

Askling HH, Bruneel F, Burchard G, Castelli F, Chiodini PL, Grobusch MP, Lopez-Vélez R, Paul M, et al; European Society for Clinical Microbiology and Infectious Diseases Study Group on Clinical Parasitology. Management of imported malaria in Europe. Malar J 2012;11: 328. PubMed PMID: 22985344.

(Recommendations on treatment of malaria from a European panel; atovaquone-proguanil is a first line treatment for uncomplicated P. falciparum malaria; side effects of ALT elevations and hepatotoxicity are not mentioned).

Kimura M, Koga M, Kikuchi T, Miura T, Maruyama H. Efficacy and safety of atovaquone-proguanil in treating imported malaria in Japan: the second report from the research group. Parasitol Int 2012; 61: 466-9. PubMed PMID: 22484597.

(30 cases of P. falciparum or vivax malaria in Japan were treated successfully with atovaquone-proguanil; one patient with P. falciparum had abnormal liver tests [bilirubin 2.0 mg/dL, ALT 294 U/L] with thrombocytopenia [48,000/μL] that resolved within 4 weeks of stopping treatment).

Cordel H, Cailhol J, Matheron S, Bloch M, Godineau N, Consigny PH, Gros H, et al. Atovaquone-proguanil in the treatment of imported uncomplicated Plasmodium falciparum malaria: a prospective observational study of 553 cases. Malar J 2013; 12: 399. PubMed PMID: 24200190.

(Among 553 French travelers treated for uncomplicated malaria with atovaquone-proguanil, parasitemia cleared in all patients by day 7 and only 3 patients relapsed; side effects included nausea or vomiting [17%], headache [7%], and rash [2%]. "As observed in the literature, this study did not reveal any liver toxicity").

Hernández N, Bessone F, Sánchez A, di Pace M, Brahm J, Zapata R, A Chirino R, et al. Profile of idiosyncratic drug induced liver injury in Latin America: an analysis of published reports. Ann Hepatol 2014; 13: 231-9. PubMed PMID: 24552865.

(Among 176 reports of drug induced liver injury from Latin America published between 1996 and 2012, none were attributed to an antimalarial agent).

Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterology 2013; 144: 1419-25. (In a PubMed PMID: 23419359.

population based study from Iceland, 96 cases of drug induced liver injury were identified over a 2 year period [2010 and 2011], but none were attributed to an antimalarial agent).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, none were attributed to an antimalarial agent).

Advice for travelers. Treat Guidel Med Lett 2015: 57 (1466): 52-8. PubMed PMID: 25853663.

(Concise guidelines on prevention of malaria in travelers indicates that atovaquone-proguanil taken once daily is an effective prophylaxis against choloroquine resistant Plasmodium species, "...generally the best tolerated

prophylactic, but it can cause headache, insomnia, GI disturbances and mouth ulcers, and is expensive. Single case reports of Stevens Johnson syndrome and hepatitis have been published").