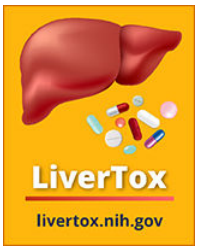
U.S. National Library of Medicine
National Center for Biotechnology Information

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-. Miltefosine. [Updated 2017 Mar 15].
Bookshelf URL: https://www.ncbi.nlm.nih.gov/books/



Miltefosine

Updated: March 15, 2017.

OVERVIEW

Introduction

Miltefosine is an orally available, alkyl phospholipid that is used in the treatment of both cutaneous and visceral leishmaniasis. Miltefosine therapy is often accompanied by transient mild-to-moderate serum aminotransferase elevations during the first 1 or 2 weeks of treatment, but has not been implicated in cases of clinically apparent liver injury with jaundice.

Background

Miltefosine (mil" te foe' sin) is an alkylated phosphocholine that has in vitro and in vivo activity against several bacteria, fungi and parasites including several Leishmania species. Miltefosine appears to act by affecting phospholipid membrane integrity and mitochondria function of the microorganism. Miltefosine has been shown to be effective in inducing cures of visceral (kala azar), mucosal and cutaneous leishmaniasis in a high proportion of patients. Miltefosine was approved for use in India in 2002 and in the United States in 2014 and was the first oral therapy of visceral and cutaneous leishmaniasis. It is available as capsules of 50 mg under the commercial name Impavido. The recommended dose is 50 mg twice (body weight 30 to 44 kg) or three times (45 kg or above) daily for 28 days. Miltefosine also has been reported to be effective in other serious bacterial, fungal and parasitic conditions such as amebiasis (primary amoebic meningoencephalitis), trypanosoma cruzii infection (Chagas disease), cryptococcosis and candidiasis, but is not formally approved for these conditions. Miltefosine is generally well tolerated, but side effects can include nausea, vomiting, diarrhea, abdominal discomfort, anorexia, pruritus, headache, dizziness and somnolence. Rare, but potentially severe adverse events include decrease in reproductive capacity, embryo-fetal toxicity, renal dysfunction and hypersensitivity reactions including Stevens Johnson syndrome. While miltefosine is rarely used in the United States, it is an important medication from a worldwide perspective and has played an essential role in public health efforts to eradicate visceral and cutaneous leishmaniasis.

Hepatotoxicity

Serum aminotransferase levels are frequently elevated in patients with visceral leishmaniasis and miltefosine therapy regularly results in a decline in mean values into the normal range. In prospective studies of miltefosine therapy, however, as many as half of patients had mild-to-moderate ALT elevations during therapy, although values above 5 times ULN were rare (<1%). The serum aminotransferase elevations were transient, generally arising during the first few weeks of therapy and ultimately resolving without dose adjustments or drug interruptions. There have been no case reports of clinically apparent liver injury with jaundice attributed to miltefosine therapy. Thus, significant liver injury from miltefosine must be very rare, if it occurs at all.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The possible causes of liver injury from miltefosine therapy are not known. Miltefosine is a simple, modified phosphocholine and is metabolized in many cells. The relative toxicity of miltefosine for parasites and other microorganisms as opposed to human cells probably relates to differences in phosphocholine metabolism. It does, however, have embryo-fetal toxicity in humans. Miltefosine has no known drug-drug interactions.

Outcome and Management

The serum aminotransferase and alkaline phosphatase elevations that occur during miltefosine therapy are typically asymptomatic and self-limited and do not require dose adjustment or discontinuation. Appearance of frank jaundice or symptoms accompanying liver test abnormalities during therapy of leishmaniasis with miltefosine should lead to temporary discontinuation and careful search for other possible causes of liver injury.

Drug Class: Antiinfective Agents, Leishmaniasis Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Miltefosine – Impavido®

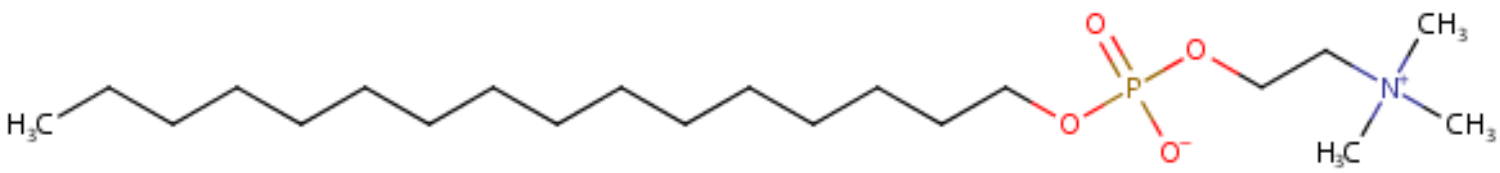
DRUG CLASS

Antiinfective Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Miltefosine	58066-85-6	C21-H46-N-O4-P	

ANNOTATED BIBLIOGRAPHY

References updated: 15 March 2017

Zimmerman HJ. Hepatic injury from the treatment of infectious and parasitic diseases. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999. pp 589-637.

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

Moseley RH. Antibacterial and Antifungal Agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd Edition. Amsterdam: Elsevier, 2013. p. 463-81.

(Review of hepatotoxicity of antibiotics; miltefosine is not discussed).

Sundar S, Rosenkaimer F, Makharia MK, Goyal AK, Mandal AK, Voss A, Hilgard P, Murray HW. Trial of oral miltefosine for visceral leishmaniasis. Lancet 1998; 352(9143): 1821-3. PubMed PMID: 9851383.

(Among 30 Indian men with visceral leishmaniasis treated with one of six dose regimens of oral miltefosine [50 mg every other day to 250 mg daily] for 28 days, all responded to therapy and 21 were cured; side effects included vomiting, diarrhea and renal insufficiency and were severe in the highest dose groups; no mention of ALT elevations or hepatotoxicity).

Sundar S, Jha TK, Thakur CP, Engel J, Sindermann H, Fischer C, Junge K, et al. Oral miltefosine for Indian visceral leishmaniasis. N Engl J Med 2002; 347: 1739-46. PubMed PMID: 12456849.

(Among 299 Indian patients [age above 12 years] with visceral leishmaniasis treated with miltefosine [50 or 100 mg by mouth daily for 28 days] or amphotericin B [1 mg/kg intravenously every other day for 30 days], long term cure rates were 94% vs 96% and side effects of miltefosine included vomiting [38%], diarrhea [20%], and ALT elevations [51%] that were above 5 times ULN in only 1 patient [<1%]; no discontinuations for liver test abnormalities, but one patient developed Stevens Johnson syndrome).

Singh UK, Prasad R, Kumar R, Jaiswal BP. Miltefosine in children with visceral leishmaniasis. Indian Pediatr 2006; 43: 1076-80. PubMed PMID: 17202605.

(Among 64 Indian children with visceral leishmaniasis treated with miltefosine for 28 days, the 6 month cure rate was 97% and side effects included ALT elevations above 3 times ULN in 61%, but all were asymptomatic and transient and did not require dose adjustment).

Sundar S, Jha TK, Thakur CP, Bhattacharya SK, Rai M. Oral miltefosine for the treatment of Indian visceral leishmaniasis. Trans R Soc Trop Med Hyg 2006; 100 Suppl 1: S26-33. PubMed PMID: 16730038.

(Review of the efficacy and safety of miltefosine in visceral leishmaniasis: "although 55% of patients had a slight asymptomatic rise in hepatic transaminase during the early treatment phase [week 1], values decreased to less than base-line values by week 2").

Soto J, Toledo J, Valda L, Balderrama M, Rea I, Parra R, Ardiles J, et al. Treatment of Bolivian mucosal leishmaniasis with miltefosine. Clin Infect Dis 2007; 44: 350-6. PubMed PMID: 17205440.

(Among 72 patients with Bolivian mucosal leishmaniasis [L. braziliensis] treated with miltefosine [2.5 mg/kg/day] for 28 days, the 12 month cure rate was 83% for mild cases [limited to nose and nasal mucosa] and 58% for more extensive cases [palate, pharynx, larynx], while side effects included mild, asymptomatic AST elevations [peak value 39 U/L] with no change in mean values).

Bhattacharya SK, Sinha PK, Sundar S, Thakur CP, Jha TK, Pandey K, Das VR, et al. Phase 4 trial of miltefosine for the treatment of Indian visceral leishmaniasis. J Infect Dis 2007; 196: 591-8. PubMed PMID: 17624846.

(Open label trial of outpatient administration of oral miltefosine in 1132 adult and pediatric Indian patients with visceral leishmaniasis; the cure rate was 96% among the 971 who returned for follow up evaluation and adverse events included vomiting [8%], diarrhea [6%] and ALT elevations which were mild and occurred early, while mean ALT and AST values decreased with treatment).

Machado PR, Ampuero J, Guimarães LH, Villasboas L, Rocha AT, Schriefer A, Sousa RS, et al. Miltefosine in the treatment of cutaneous leishmaniasis caused by Leishmania braziliensis in Brazil: a randomized and controlled trial. PLoS Negl Trop Dis 2010; 4: e912. PubMed PMID: 21200420.

(Among 90 Brazilian patients [ages 2-65 years] with cutaneous leishmaniasis [L. braziliensis] treated with oral miltefosine vs intravenous pentavalent antimony, the cure rate was 75% vs 53% and side effects of miltefosine included vomiting [42%], nausea [40%], diarrhea [10%] and abdominal pain [23%]; no mention of ALT values or hepatoxicity).

Oliveira LF, Schubach AO, Martins MM, Passos SL, Oliveira RV, Marzochi MC, Andrade CA. Systematic review of the adverse effects of cutaneous leishmaniasis treatment in the New World. Acta Trop 2011; 118: 87-96. PubMed PMID: 21420925.

(Review of the adverse events associated with various therapies of cutaneous leishmaniasis including miltefosine; mentions the adverse effects of mild-to-moderate aminotransferase and creatinine elevations).

Chrusciak-Talhari A, Dietze R, Chrusciak Talhari C, da Silva RM, Gadelha Yamashita EP, de Oliveira Penna G, Lima Machado PR, et al. Randomized controlled clinical trial to access efficacy and safety of miltefosine in the treatment of cutaneous leishmaniasis caused by Leishmania (Viannia) guyanensis in Manaus, Brazil. Am J Trop Med Hyg 2011; 84: 255-60.

(Among 90 patients [ages 4-59 years] with cutaneous leishmaniasis treated with oral miltefosine or parenteral antimony, the cure rate was 71% vs 54% and adverse events of miltefosine included vomiting [48%], nausea [9%], diarrhea [7%] and ALT elevations [10%] that were mild and resolved without dose modification).

Dorlo TP, Balasegaram M, Beijnen JH, de Vries PJ. Miltefosine: a review of its pharmacology and therapeutic efficacy in the treatment of leishmaniasis. J Antimicrob Chemother 2012; 67: 2576-97. PubMed PMID: 22833634.

(Review of the pharmacology and mechanism of action of miltefosine suggests that the steroid and fatty acid metabolism of the protozoan parasite is the major target of the anti-leishmaniasis activity).

Magerl M, Rother M, Bieber T, Biedermann T, Brasch J, Dominicus R, Hunzelmann N, et al. Randomized, double-blind, placebo-controlled study of safety and efficacy of miltefosine in antihistamine-resistant chronic spontaneous urticaria. J Eur Acad Dermatol Venereol 2013; 27: e363-9. PubMed PMID: 22928719.

(Among 73 patients with chronic idiopathic urticaria treated with miltefosine [50-150 mg daily] or placebo for 28 days, urticaria symptoms were less with miltefosine and side effects were generally mild with no serious adverse events and "no relevant changes" in laboratory test results).

Miltefosine (Impavido) for leishmaniasis. Med Lett Drugs Ther 2014; 56 (1451): 89-90. PubMed PMID: 25211304.

(Concise review of leishmaniasis and therapy with miltefosine including efficacy, safety and costs; mentions that elevations in aminotransferases and creatinine can occur with treatment).

Ostyn B, Hasker E, Dorlo TP, Rijal S, Sundar S, Dujardin JC, Boelaert M. Failure of miltefosine treatment for visceral leishmaniasis in children and men in South-East Asia. PLoS One 2014; 9): e100220. PubMed PMID: 24941345.

(Among 1016 Indian patients with visceral leishmaniasis treated with miltefosine for 28 days at 7 health centers, the cure rate was 94% at end of therapy and 86% 6 months later; comparisons of relapse [n=78] versus nonrelapse

subjects [n=775] showed relapses were more frequent in men vs women [11% vs 6%] and children vs adults [12-16% vs 6%], but not with side effects vs without).

Vakil NH, Fujinami N, Shah PJ. Pharmacotherapy for leishmaniasis in the United States: focus on miltefosine. Pharmacotherapy 2015; 35: 536-45. PubMed PMID: 25940658.

(Review of the pharmacotherapy available for leishmaniasis in the US including pentavalent antimonials, pentamidine, amphotericin and miltefosine, the only oral therapy and one that has only recently become available, with common adverse effects being vomiting, diarrhea and transient liver enzyme level elevations).

Georgiadou SP, Makaritsis KP, Dalekos GN. Leishmaniasis revisited: Current aspects on epidemiology, diagnosis and treatment. J Transl Int Med 2015; 3: 43-50. PubMed PMID: 27847886.

(Review of the epidemiology, diagnosis and treatment of leishmaniasis).

van der Snoek EM, Couwenberg SM, Stijnis C, Kortbeek LM, Schadd EM. Two cases of cutaneous leishmaniasis in Dutch military personnel treated with oral miltefosine. J R Army Med Corps 2017; 163: 68-70. PubMed PMID: 26661280.

(Two Dutch citizens with cutaneous leishmaniasis acquired in Belize [L. braziliensis] and a Balearic island [L. donovani] were treated with miltefosine [50 mg three times daily for 28 days] and both had a beneficial response with mild creatinine elevations during therapy, but no changes in serum aminotransferase levels).