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Ivermectin

Updated: April 27, 2018.

OVERVIEW

Introduction

Ivermectin is an antiinfective agent with activity against several parasitic nematodes and scabies and is the treatment of choice for onchocerciasis (river blindness). It is typically given as one or two oral doses. Ivermectin therapy has been associated with minor, self-limiting serum aminotransferase elevations and very rare instances of clinically apparent liver injury.

Background

Ivermectin (eye" ver mek" tin) is a macrocyclic lactone and semisynthetic derivative of avermectin which is produced by Streptomyces avermitilis. Ivermectin has potent activity against several parasites and arthropods. It believed to act by interference with a glutamate gated chloride channel, which interferes with the parasite's neural and neuromuscular transmission. It has a broad spectrum of activity against several nematodes (Ascaris, Trichuris, Ancylostoma), cestodes (Taenia) and trematodes (Fasciola, Schistosoma). Ivermectin has particularly potent activity against onchocerciasis (river blindness) and lymphatic filariasis, which are important endemic diseases in Africa and South America. Ivermectin was approved for use in the United States in 1996 for strongyloidiasis and onchocerciasis. In other countries it is also approved for use in scabies, lice infestation and ascariasis. Ivermectin is available in tablets of 3 mg under the brand name Stromectol. For treatment of strongyloidiasis, the recommended dose for adults is a single oral dose of 15 mg (200 μg/kg). Ivermectin is also available in topical forms for therapy of rosacea and head lice. Oral ivermectin is generally well tolerated, but side effects can include diarrhea, gastrointestinal upset, headaches, fever, rash and itching, most of which are due to the effect of ivermectin on the helminth and a reaction to their death, release and expulsion.

Hepatotoxicity

Single dose therapy with ivermectin has been associated with a low rate of serum aminotransferase elevations. A single case of clinically apparent liver injury has been reported after ivermectin use (Case 1). The onset of injury occurred 1 month after a single dose and was characterized by a hepatocellular pattern of serum enzyme elevations without jaundice. Recovery was rapid and complete.

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

Mechanism of Injury

Ivermectin acts by interference with chloride channels that are important in neuromuscular activity in parasitic worms and protozoa, but has little activity against mammalian neural transmission. The mechanism by which it might cause liver injury is unknown.

Outcome and Management

Ivermectin is usually well tolerated and the liver injury reported with its use has been mild and self-limited in course. Ivermectin has not been associated with acute liver failure or chronic liver injury.

Drug Class: Antihelmintic Agents

CASE REPORT

Case 1. Acute liver injury due to ivermectin.

[Modified from: Veit O, Beck B, Steuerwald M, Hatz C. First case of ivermectin-induced severe hepatitis. Trans R Soc Trop Med Hyg 2006; 100: 795-7. PubMed Citation]

A 20 year old woman from the Cameroon who had been living in Switzerland for 5 years was found to have a migrating worm in her right sclera which was removed and identified as Loa loa. She had eosinophilia (18.5%) and microfilaraemia and was treated with albendazole (600 mg daily) for 21 days. She subsequently had reduced but continued low levels of microfilia in the blood and three months later was treated with a single dose of ivermectin (15 mg orally). One month later, when seen for routine follow up, she complained of abdominal pain, and serum aminotransferase levels, which had been normal, were markedly elevated (Table). Serum bilirubin and alkaline phosphatase levels were normal. She had no history of liver disease or known risk factors for viral hepatitis other than country of origin. She did not drink alcohol and was not taking other medications, over-the-counter products or herbals. Tests for hepatitis A, B, and C and Epstein Barr virus infection were negative. A liver biopsy showed acute hepatocellular necrosis, apoptotic bodies, lymphocytic lobular infiltrates and no fibrosis. She improved clinically within days and serum aminotransferase levels fell rapidly, becoming normal three months later. Because of continuing low levels of microfiliariaemia, she was treated with diethylcarbamazine for 29 days with subsequent loss of microfilariae and no further problems or serum enzyme elevations.

Key Points

Medication:	Ivermectin (15 mg, single dose)
Pattern:	Hepatocellular (R=21.6)
Severity:	1+ (serum enzyme elevations without jaundice)
Latency:	1 month
Recovery:	3 months
Other medications:	None in immediate previous 2 months

Laboratory Values

Time After Starting	ALT (U/L)	Alk P (U/L)	Bilirubin* (mg/dL)	Other
Pre	21	58	0.6	Albendazole for 21 days
0	35	40	0.5	Ivermectin one dose

Table continued from previous page.

Time After Starting	ALT (U/L)	Alk P (U/L)	Bilirubin* (mg/dL)	Other
1 month	907	61	1.3	
2 months	111	57	1.0	
3 months	54	43	1.2	
6 months	13	38	0.8	
Normal	**<42**	**<126**	**<1.2**	

* Converted from µmol/L.

Comment

Without routine monitoring this mild case of anicteric hepatitis might have gone unrecognized. Because most studies of antiheminthic therapies have been done without routine monitoring of liver tests, the true rate of liver injury and even clinically apparent liver disease due to these agents may be underappreciated. On the other hand, this episode of acute hepatitis may have been due to an unrelated incurrent illness (hepatitis E for instance). Because the reaction occurred after a single dose of ivermectin, however, rechallenge would not be appropriate.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Ivermectin – Stromectol®

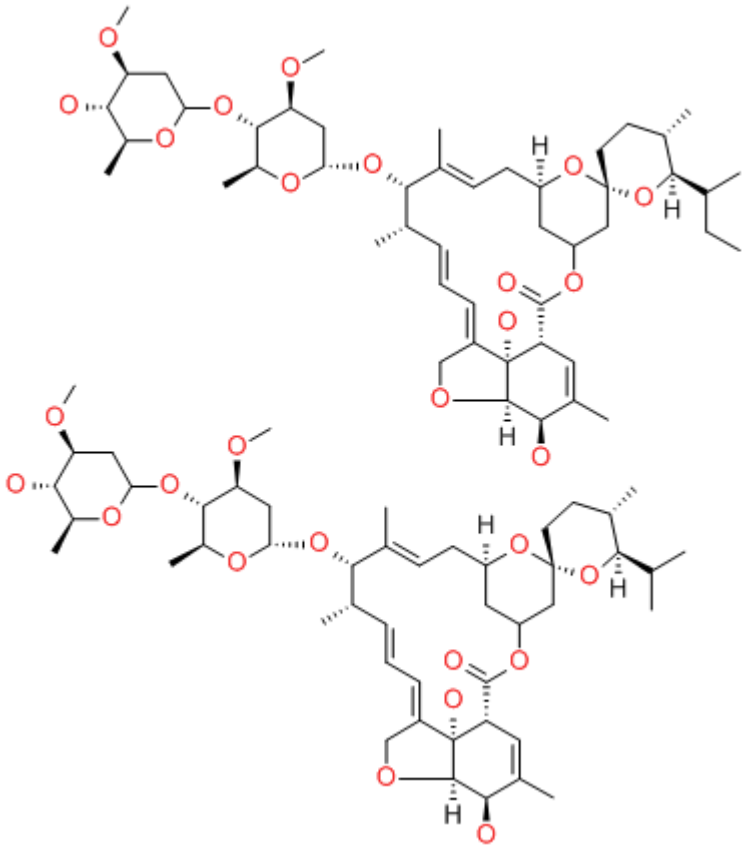
DRUG CLASS

Antihelmintic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Ivermectin	70288-86-7	C48-H74-O14 and C47-H72-O14	

ANNOTATED BIBLIOGRAPHY

References updated: 27 April 2018

Zimmerman HJ. Antihelminthics. Hepatic injury from antimicrobial agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 626-8.

(Expert review of hepatotoxicity of antihelminthics written in 1999; ivermectin is not discussed).

McCarthy J, Loukas A, Hotez PJ. Chemotherapy of helminth infections. In, Brunton LL, Chabner KA, Knollman KC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. Amsterdam: Elsevier, 2011, pp.1443-61.

(Textbook of pharmacology and therapeutics; ivermectin is a semisynthetic avermectin, a novel class of macrocyclic lactones with activity against nematodes and arthropods and commonly used in veterinary medicine).

Shikiya K, Zaha O, Niimura S, Uehara T, Ohshiro J, Kinjo F, Saito A, et al. [Clinical study on ivermectin against 125 strongyloidiasis patients]. Kansenshogaku Zasshi 1994; 68: 13-20. Japanese. PubMed PMID: 8138669.

(Abstract only: among 125 patients with strongyloidiasis treated with ivermectin [6 mg, 2 oral doses 2 weeks apart], 14% had serum enzyme elevations, but all were self-limiting and asymptomatic).

Gardon J, Gardon-Wendel N, Cemanga-Ngangue, Kamgno J, Chippaux JP, Boussinesq M. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infection. Lancet 1997; 350: 18-22. PubMed PMID: 9217715.

(In a mass treatment program for onchocerciasis, 0.1% of 17,877 people treated developed severe reactions including neurological impairment and one death; reactions correlated with high pretreatment L. loa microfilareamia counts; no mention of jaundice or hepatitis).

Dunyo SK, Nkrumah FK, Simonsen PE. A randomized double-blind placebo-controlled field trial of ivermectin and albendazole alone and in combination for the treatment of lymphatic filariasis in Ghana. Trans R Soc Trop Med Hyg 2000; 94: 205-11. PubMed PMID: 10897370.

(Placebo controlled trial of ivermectin, albendazole or the combination in 1425 persons from filariasis-endemic villages; showed clear reduction in microfilarial levels with ivermectin alone or in combination; side effects were mild and self-limited, no mention of liver injury).

Zaha O, Hirata T, Kinjo F, Saito A, Fukuhara H. Efficacy of ivermectin for chronic strongyloidiasis: two single doses given 2 weeks apart. J Infect Chemother 2002; 8: 94-8. PubMed PMID: 11957127.

(50 patients with strongyloides infection were treated with two single doses of ivermectin; 98% efficacy and mild side effects only, 1 patient had minimal, transient ALT elevation [40 U/L]).

Guzzo CA, Furtek CI, Porras AG, Chen C, Tipping R, Clineschmidt CM, Sciberras DG, et al. Safety, tolerability, and pharmacokinetics of escalating high doses of ivermectin in healthy adult subjects. J Clin Pharmacol 2002; 42: 1122-33. PubMed PMID: 12362927.

(Multiple, escalating dose [30-120 mg] study of ivermectin; side effects were mild, transient and no more common than with placebo; 2% of 51 ivermectin- vs 6% of 17 placebo-recipients had transient ALT elevations [2-2.5 times ULN]).

Veit O, Beck B, Steuerwald M, Hatz C. First case of ivermectin-induced severe hepatitis. Transact Royal Soc Trop Med Hygiene 2006; 100: 795-7. PubMed PMID: 16682062.

(20 year old Cameroon woman with L. Loa infection developed symptoms and serum aminotransferase elevations 1 month after single dose of ivermectin [bilirubin 1.3 mg/dL, AL 907 U/L, Alk P 61 U/L], resolving in next 3 months: Case 1).

Sparsa A, Bonnetblanc JM, Peyrot I, Loustaud-Ratti V, Vidal E, Bédane C. [Systemic adverse reactions with ivermectin treatment of scabies]. Ann Dermatol Venereol 2006; 133: 784-7. French. PubMed PMID: 17072195.

(72 year old man developed nausea and abdominal pain 3 days after single dose of ivermectin for scabies with ALT 2.5 times ULN, with resolution in 2 weeks; no mention of bilirubin).

Chalasani N, Fontana RJ, Bonkovsky HL, Watkins PB, Davern T, Serrano J, Yang H, Rochon J; Drug Induced Liver Injury Network (DILIN). Causes, clinical features, and outcomes from a prospective study of drug-induced liver injury in the United States. Gastroenterology 2008; 135: 1924-34. PubMed PMID: 18955056.

(Among 300 cases of drug induced liver disease collected in the US between 2003 and 2008, none were attributed to an antihelmintic agent).

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 antihelmintic agents]).

Ferrajolo C, Capuano A, Verhamme KM, Schuemie M, Rossi F, Stricker BH, Sturkenboom MC. Drug-induced hepatic injury in children: a case/non-case study of suspected adverse drug reactions in VigiBase. Br J Clin Pharmacol 2010; 70: 721-8. PubMed PMID: 21039766.

(Worldwide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, none of which were attributed to an antihelmintic agent).

Drugs for parasitic infections. Treat Guidelines Med Ltr 2010; 8: 1-20. Not in PubMed

(Brief description of drugs for parasitic infections in adults and children as well as a table of their major side effects; ivermectin is useful in treatment of ascariasis, cutaneous larva migrans, filariasis, lice infestation, strongyloidiasis, and trichuriasis).

Muñoz J, Ballester MR, Antonijoan RM, Gich I, Rodríguez M, Colli E, Gold S, Krolewiecki AJ. Safety and pharmacokinetic profile of fixed-dose ivermectin with an innovative 18mg tablet in healthy adult volunteers. PLoS Negl Trop Dis 2018; 12: e0006020. PubMed PMID: 29346388.

(Pharmacokinetic study compared fixed doses of ivermectin [16 or 32 mg] vs weight-based doses in 57 healthy volunteers, found equivalent plasma levels with all doses and there were no adverse events).

Barda B, Sayasone S, Phongluxa K, Xayavong S, Keoduangsy K, Odermatt P, Puchkov M, Huwyler J, Hattendorf J, Keiser J. Efficacy of moxidectin versus ivermectin against Strongyloides stercoralis infections: a randomized, controlled noninferiority trial. Clin Infect Dis 2017; 65: 276-81. PubMed PMID: 28369530.

(Among 127 subjects wtih Strongyloides stercoralis infection treated with a single dose of moxidectin or ivermectin, response rates were 94% and 95%, adverse event rates were similar and "none of the participants reported any side effect from treatment at any time point").

Kircik LH, Del Rosso JQ, Layton AM, Schauber J. Over 25 Years of Clinical Experience With Ivermectin: An overview of safety for an increasing number of indications. J Drugs Dermatol 2016; 15: 325-32. PubMed PMID: 26954318.

(Ivermectin has been used for more than 25 years for an expanding number of helmintic infections with an excellent safety profile both in humans and other mammals, probably because of its high specificity for invertibrate neuronal ion channels and because it does not cross the human blood-brain barrier; no mention of hepatotoxicity or ALT elevations).

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, no cases were attributed to ivermectin).

Ouédraogo AL, Bastiaens GJ, Tiono AB, Guelbéogo WM, Kobylinski KC, Ouédraogo A, Barry A, et al. Efficacy and safety of the mosquitocidal drug ivermectin to prevent malaria transmission after treatment: a double-blind, randomized, clinical trial. Clin Infect Dis 2015; 60: 357-65. PubMed PMID: 25414262.

(Among 120 patients with Plasmodium falciparum infection given a single or repeated dose of artemether-lumefantrine with or without ivermectin, and no serious adverse events or "significant" biochemical abnormalities arose).