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Lansoprazole

Updated: April 15, 2019.

OVERVIEW

Introduction

Lansoprazole is a proton pump inhibitor (PPI) and a potent inhibitor of gastric acidity which is widely used in the therapy of gastroesophageal reflux and peptic ulcer disease. Dexlansoprazole is an isomer of lansoprazole that has a similar spectrum of activity and toxicities. Lansoprazole therapy is associated with a low rate of transient and asymptomatic serum aminotransferase elevations and is a reported, but very rare cause of clinically apparent liver injury.

Background

Lansoprazole (lan soe' pra zole), like other PPIs, binds to and inactivates the hydrogen/ potassium (H+/K+) ATPase of gastric parietal cells, causing inhibition of the proton pump that transports H+ into the gastric lumen, the final common step in gastric acid production. Lansoprazole is a prodrug and is converted to the active form in the acidic secretory canaliculi of parietal cells. Because the inhibition is irreversible, acid secretion is suppressed for 24 to 48 hours, until new proton pump molecules have been synthesized and transported to the cell membrane. Lansoprazole was the second PPI approved for use in the United States (1995) and dexlansoprazole, a stereoisomer, was approved for use in 2009. Lansoprazole is available in 15 and 30 mg delayed release capsules and tablets, as well as granules for oral suspension and in vials for parenteral use under the brand name of Prevacid. Over-the-counter formulations have also become available. The typical dose in adults with peptic ulcer disease is 15 mg daily for 4 to 8 weeks and similar dose chronically for maintenance therapy. Higher doses are recommended for more severe cases of gastrointestinal reflux and peptic ulcer disease, and doses of up to 120 mg daily for Zollinger-Ellison syndrome. Combinations of lansoprazole with antibiotics for 10 to 14 days are effective and recommended for eradication of H. pylori infection. Dexlansoprazole is available by prescription only in capsules of 30 or 60 mg under the brand name Dexilant. The recommended dose of dexlansoprazole is 30 to 60 mg once daily. Both lansoprazole and dexlanscprazole are very well tolerated. Side effects are uncommon and usually mild: they can include diarrhea, nausea, vomiting, abdominal discomfort, flatulence, skin rash, headaches and dizziness. Severe adverse events are rare but can include hypersensitivity reactions. Long-term use may be associated with bone fractures, acute interstitial nephritis, lupus erythematosus, vitamin B12 deficiency and hypomagnesemia.

Hepatotoxicity

Despite its wide use, lansoprazole has only rarely been associated with hepatic injury. In large scale, long term trials of lansoprazole, serum ALT elevations have occurred in less than 1% of patients and at rates similar to those that occur with placebo or comparator drugs. Only a small number of cases of clinically apparent liver

disease due to lansoprazole or dexlansoprazole have been published and most have been anicteric and mild. In most instances, the time to onset was within 2 to 4 weeks and the pattern of enzyme elevations was hepatocellular or mixed. Hypersensitivity reactions with fever, rash and eosinophilia have been described due to dexlansoprazole and lansoprazole, and these reactions may be accompanied by minor serum enzyme elevations and thus qualify for DRESS syndrome (drug-rash with eosinophilia and systemic symptoms). Autoantibody formation is rare. Recovery is usually rapid (within a month) and complete upon stopping lansoprazole. Recurrence on reexposures has been reported.

Likelihood score: C (probable rare cause of clinically apparent liver injury).

Mechanism of Injury

Several features of the hepatic injury with lansoprazole suggest a hypersensitivity reaction, but may merely reflect altered metabolism or acute toxicity of a metabolic byproduct. Lansoprazole is metabolized by the hepatic P450 system, but has little effect on the activity of the drug-metabolizing enzymes.

Outcome and Management

The mild and asymptomatic elevations in serum aminotransferase that have been observed during lansoprazole therapy are usually transient and usually resolve even without dose modification. Clinically apparent liver injury due to dexlansoprazole and lansoprazole, however, generally calls for prompt withdrawal of the agent. Severe injury is uncommon and most cases resolve promptly upon withdrawal. Cases of acute liver failure due proton pump inhibitors have been described, but they are exceedingly rare. There is no information about cross reactivity among the various PPIs after lansoprazole hepatotoxicity, but the PPIs all share a benzimidazole structure, and caution should be used in attempting to reintroduce another PPI after clinically apparent PPI-associated hepatic injury.

Drug Class: Antiulcer Agents

Other Drugs in the Subclass, Proton Pump Inhibitors: Esomeprazole, Omeprazole, Pantoprazole, Rabeprazole

CASE REPORT

Case 1. Acute hepatitis attributed to lansoprazole.

[Modified from: Viana de Miguel C, Alvarez García M, Sánchez Sánchez A, Carvajal García-Pando A. [Lansoprazole-induced hepatitis]. Med Clin (Barc) 1997; 108: 599. Spanish. PubMed Citation]

A 62 year old man with gastroesophageal reflux disease developed fatigue and jaundice 25 days after switching from omeprazole (20 mg daily for 3 months) to lansoprazole (30 mg daily). He had no history of drug reactions, liver disease, jaundice, alcohol abuse or risk factors for viral hepatitis. Laboratory testing showed marked elevations in serum bilirubin (26.0 mg/dL) and aminotransferase levels (ALT 1498 U/L, AST 952 U/L), and mild elevations in alkaline phosphatase (346 U/L: normal values not given). Tests for hepatitis A, B, and C were negative and abdominal ultrasound showed a single gallstone without evidence of biliary obstruction. A liver biopsy was compatible with acute toxic hepatitis. Lansoprazole was discontinued promptly upon admission and he improved rapidly, all liver tests being normal when he was seen 50 days later.

Key Points

Medication:	Lansoprazole (30 mg daily)
Pattern:	Hepatocellular (R=~12.5)
Severity:	3+ (jaundice, hospitalization)

Table continued from previous page.

Latency:	25 days
Recovery:	50 days
Other medications:	None mentioned

Comment

This brief letter to the editor describes one of the few cases of lansoprazole associated liver injury in the literature. The onset of injury was within 4 weeks of starting lansoprazole, which is typical of proton-pump inhibitor associated acute liver injury, as was the hepatocellular pattern of serum enzyme elevations. Symptoms of hypersensitivity were not mentioned nor were autoantibody test results given, but the pattern otherwise resembles the clinically apparent liver injury associated with PPIs. Interestingly, this patient had tolerated omeprazole therapy for 3 months without problems, suggesting that there is little cross reactivity to hepatic injury among the proton pump inhibitors. Unfortunately, this cannot be assumed for all such agents and caution should be used in restarting another proton pump inhibitor after clinical apparent liver injury due to another.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Lansoprazole – Generic, Prevacid®

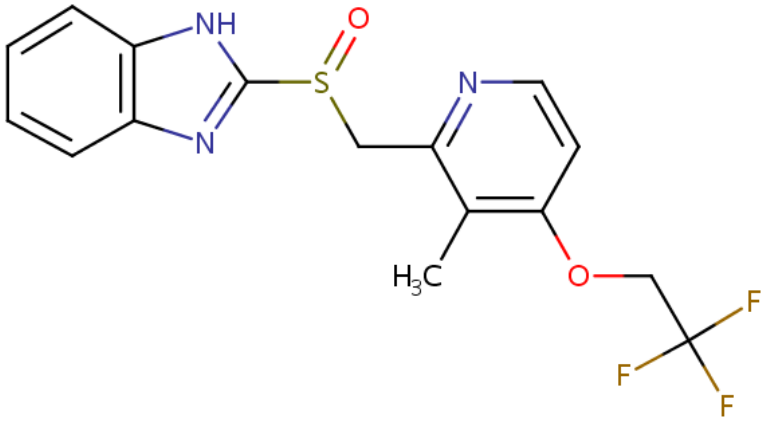
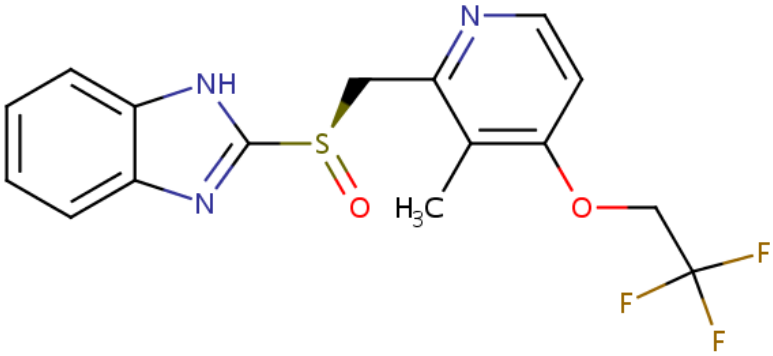
DRUG CLASS

Antiulcer Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Lansoprazole	103577-45-3	C16-H14-F3-N3-O2-S	
Dexlansoprazole	138530-94-6	C16-H14-F3-N3-O2-S	

ANNOTATED BIBLIOGRAPHY and Dexlansoprazole

References updated: 15 April 2019

Zimmerman HJ. Proton pump inhibitors. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 720-1.

(Expert review of hepatotoxicity published in 1999 states that aminotransferase elevations occur in ~1% of PPI treated patients, but only 1 case of acute liver injury has been reported with omeprazole, none with the more recently released lansoprazole and pantoprazole).

Sharkey KA, McNaughton WK. Pharmacotherapy of gastric acidity, peptic ulcers, and gastroesophageal reflux disease. In, Brunton LL, Hilal-Dandan R, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 909-20.

(Textbook of pharmacology and therapeutics).

Arnold R. Safety of proton pump inhibitors - an overview. Aliment Pharmacol Ther 1994; 8 Suppl 1: 65-70. PubMed PMID: 8180297.

(Side effects of PPIs are uncommon and no more frequent than with cimetidine and ranitidine; "Omeprazole had no clinically relevant effects on laboratory values including...liver function").

Viana de Miguel C, Alvarez García M, Sánchez Sánchez A, Carvajal García-Pando A.. [Lansoprazole-induced hepatitis]. Med Clin (Barc) 1997; 108: 599. Spanish. PubMed PMID: 9280798.

(62 year old man developed fatigue and jaundice 25 days after switching from omeprazole [given for 3 months] to lansoprazole [bilirubin 26.0 mg/dL, ALT 1498 U/L, Alk P 346 U/L], biopsy showed toxic hepatitis, resolving in 50 days: Case 1).

Baudot S, Milpied-Homsi B, Andres P, Poirier Y, Larousse C. [Lansoprazole hypersensitivity syndrome]. Therapie 1999; 54: 491-3. French. PubMed PMID: 10667118.

(41 year old developed rash 4 weeks after switching from omeprazole to lansoprazole, followed a week later by generalized erythema, fever, fatigue, and lymphadenopathy, with ALT 4 times ULN and eosinophilia [bilirubin levels not given]; PPIs were stopped and high dose corticosteroids started, prednisone therapy lasting 8 months).

Reilly JP. Safety profile of the proton-pump inhibitors. Am J Health Syst Pharm 1999; 56 (23 Suppl 4): S11-7. PubMed PMID: 10597119.

(Review of side effects of proton pump inhibitors including long term tolerance).

Martin RM, Dunn NR, Freemantle S, Shakir S. The rates of common adverse events reported during treatment with proton pump inhibitors used in general practice in England: cohort studies. Br J Clin Pharmacol 2000; 50: 366-72. PubMed PMID: 11012560.

(Prescription event monitoring of common side effects of omeprazole, lansoprazole and pantoprazole from the UK found low rates of diarrhea [0.18-0.39/1000 days], abdominal pain [0.17-.21], nausea [0.16-0.22] and headache [0.10-0.17]; no analysis of liver toxicities).

Matheson AJ, Jarvis B. Lansoprazole: an update of its place in the management of acid-related disorders. Drugs 2001; 61: 1801-33. PubMed PMID: 11693467.

(Review of pharmacology, clinical efficacy and safety of lansoprazole; in studies of more than 30,000 patients, most common side effects are diarrhea, nausea, headache and abdominal pain; no discussion of ALT elevations or hepatotoxicity).

García-Cortés M, Lucena MI, Andrade RJ, Romero-Gómez M, Fernández MC. Lansoprazole-induced hepatic dysfunction. Ann Pharmacother 2003; 37: 1731. PubMed PMID: 14626292.

(Two cases of enzyme elevations without jaundice [one symptomatic] arising in 33 and 47 year olds, 20 and unknown days after starting lansoprazole [bilirubin 1.0 and 0.96 mg/dL, ALT 228 and 246 U/L, Alk P 110 and 361 U/L], resolving in 1-3 months; the asymptomatic patient restarted lansoprazole and had recurrence of ALT elevations).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10: 1018-23. PubMed PMID: 15390328.

(Among ~50,000 liver transplants reported to UNOS between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, but none were attributed to an H2 blocker or proton pump inhibitor).

de Abajo FJ, Montero D, Madurga M, García Rodríguez LA. Acute and clinically relevant drug-induced liver injury: a population based case-control study. Br J Clin Pharmacol 2004; 58: 71-80. PubMed PMID: 15206996.

(Analysis of General Practice Research Database from UK on 1.6 million persons from 1994-2000 found 128 cases of drug induced liver injury [2.4/100,000 person years]; 3 cases were attributed to cimetidine for an odds ratio of 2.0 compared to controls [n=5000] which was not statistically significant; PPIs not mentioned).

Heaton NR, Edmonds EV, Francis ND, Bunker CB, Bowling JC, Morar N. Fatal toxic epidermal necrolysis due to lansoprazole. Clin Exp Dermatol 2004; 29: 612-3. PubMed PMID: 15550134.

(72 year old developed toxic epidermal necrolysis one week after starting lansoprazole with fever, heart failure and respiratory arrest; had a history of skin rash after receiving lansoprazole in the past; no liver tests reported).

Björnsson E, Jerlstad P, Bergqvist A, Olsson R. Fulminant drug-induced hepatic failure leading to death or liver transplantation in Sweden. Scand J Gastroenterol 2005; 40: 1095-101. PubMed PMID: 16165719.

(Survey of all cases of DILI with fatal outcome from Swedish Adverse Drug Reporting system from 1966-2002: 103 cases identified as highly probable, probable or possible, one case attributed to ranitidine and one to omeprazole, but none to the other antiulcer agents).

Severino G, Chillotti C, De Lisa R, Del Zompo M, Ardau R. Adverse reactions during imatinib and lansoprazole treatment in gastrointestinal stromal tumors. Ann Pharmacother 2005; 39: 162-4. PubMed PMID: 15546944.

(60 year old with gastrointestinal stromal tumors on imatinib therapy developed facial edema and Stevens Johnson syndrome 10 days after starting lansoprazole for dyspepsia; she recovered upon stopping, but rash recurred when patient restarted both medications 2 months later).

Salgueiro E, Rubio T, Hidalgo A, Manso G. Safety profile of proton pump inhibitors according to the spontaneous reports of suspected adverse reactions. Int J Clin Pharmacol Ther 2006; 44: 548-56. PubMed PMID: 17176621.

(Analysis of PPI related reports to Spanish Pharmacovigilance Database during 2004 found 58 reports of liver injury from omeprazole [n=36], lansoprazole [7], pantoprazole [12], rabeprazole [2], and esomeprazole [1], correlating somewhat with relative number of prescriptions; 82% were taking other medications; most "evolved to recovery").

Sabaté M, Ibáñez L, Pérez E, Vidal X, Buti M, Xiol X, Mas A, et al. Risk of acute liver injury associated with the use of drugs: a multicentre population survey. Aliment Pharmacol Ther 2007; 25:1401-9. PubMed PMID: 17539979.

(Population based survey of 126 cases of acute liver injury due to drugs between 1993-1999 in Spain; 8 were attributed to ranitidine alone [incidence 5.1/100,000 person years] and 5 to omeprazole alone [2.1/100,000]).

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 in the US collected between 2004 and 2008, 2 were attributed to ranitidine, none to cimetidine or the proton pump inhibitors).

Lobera T, Navarro B, Del Pozo MD, González I, Blasco A, Escudero R, Venturini M, Alarcón E. Nine cases of omeprazole allergy: cross-reactivity between proton pump inhibitors. J Investig Allergol Clin Immunol 2009; 19: 57-60. (Among 9 nonatopic women with omeprazole allergy [urticaria, angioedema within 1-4 hours of administration], 8 had positive skin tests to omeprazole and 4 to pantoprazole, but none to lansoprazole; and all but one tolerated treatment with lansoprazole whereas 3 of 3 had recurrence with omeprazole; no mention of liver test results). PubMed PMID: 19274931.

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.

(World wide pharmacovigilance database contained 9036 hepatic adverse drug reactions in children, but none were due to antiulcer medications).

Reuben A, Koch DG, Lee WM; Acute Liver Failure Study Group. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. Hepatology 2010; 52: 2065-76. PubMed PMID: 20949552.

(Among 1198 patients with acute liver failure enrolled in a US prospective study between 1998 and 2007, 133 were attributed to drug induced liver injury, but done were due to lansoprazole or other proton pump inhibitors).

Zvyaga T, Chang SY, Chen C, Yang Z, Vuppugalla R, Hurley J, Thorndike D, et al. Evaluation of six proton pump inhibitors as inhibitors of various human cytochromes P450: focus on cytochrome P450 2C19. Drug Metab Dispos 2012; 40: 1698-711. PubMed PMID: 22648560.

(Using human liver microsomes to assess P450 activity, omeprazole and esomeprazole were found to be the most potent inhibitors of 2D9 and most likely to cause clinically relevant drug-drug interactions).

Fracaroli TS, Miranda LQ, Sodré JL, Chaves M, Gripp A. Toxic epidermal necrolysis induced by lansoprazole*. An Bras Dermatol 2013; 88: 117-20. PubMed PMID: 23539016.

(23 year old woman developed rash 15 days after starting lansoprazole which spread and desquamated [liver tests not mentioned], resolving within two months after intensive care and IVIG infusions).

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. PubMed PMID: 23419359.

(In a population based study of drug induced liver injury from Iceland, 96 cases were identified over a 2 year period, but none were attributable to lansoprazole or any other antiulcer medications).

Atkins C, Maheswaran T, Rushbrook S, Kamath A. Lansoprazole-induced acute lung and liver injury: a case report. Int J Clin Pharmacol Ther 2014; 52: 1102-4. PubMed PMID: 25373140.

(61 year old woman developed jaundice and shortness of breath 10 days after starting lansoprazole [bilirubin 7.9 mg/dL, ALT 447 U/L, Alk P 267 U/L] with clinical evidence of hypersensitivity pneumonitis, both the liver and lung injury responding to high doses of prednisone with normal liver tests 1 month later).

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.

(Systematic review of literature of drug induced liver injury in Latin American countries published from 1996 to 2012 identified 176 cases, none of which were attributed to lansoprazole or other proton pump inhibitors).

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.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 3 [0.3%] were attributed to proton pump inhibitors including one each for omeprazole, esomeprazole and lansoprazole).

Lopez JL, Tayek JA. Voriconazole-induced hepatitis via simvastatin- and lansoprazole-mediated drug interactions: a case report and review of the literature. Drug Metab Dispos 2016; 44: 124-6. PubMed PMID: 26502771.

(44 year old man with Wegeners granulomatosus and pulmonary aspergillosis on long term voriconazole developed jaundice within 10 days of starting lansoprazole [bilirubin 14 mg/dL, ALT 362 U/L, Alk P 406 U/L], resolving rapidly on stopping but recurrence of jaundice 2 weeks after starting simvastatin [bilirubin 15.4 mg/dL, ALT 893 U/L, Alk P 789 U/L] while still on voriconazole; injury suspected to be due to drug-drug interactions).

Tsai CF, Chen MH, Wang YP, Chu CJ, Huang YH, Lin HC, Hou MC, Let al. Proton pump inhibitors increase risk for hepatic encephalopathy in patients With cirrhosis in a population study. Gastroenterology 2017; 152: 134-41. PubMed PMID: 27639806.

(Analysis of the Taiwan National Health Insurance database found a higher rate of proton pump inhibitor use among patients with cirrhosis who developed hepatic encephalopathy [38%: 445 of 1166] compared to a matched group with cirrhosis who did not [rate not provided]; the relative risk was raised for all agents except for rabeprazole).

Weersink RA, Bouma M, Burger DM, Drenth JPH, Froukje Harkes-Idzinga S, Hunfeld NGM, Metselaar HJ, et al. Safe use of proton pump inhibitors in patients with cirrhosis. Br J Clin Pharmacol 2018 Apr 24. Epub ahead of print]. PubMed PMID: 29688583.

(Systematic review of 69 publications in the literature suggested that doses of proton pump inhibitors should be reduced in patients with cirrhosis and only omeprazole should be used in those with Child Pugh Class C cirrhosis).