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Prochlorperazine

Updated: January 23, 2014.

OVERVIEW

Introduction

Prochlorperazine is a phenothiazine used primarily as an antiemetic agent. In rare instances, prochlorperazine can cause clinically apparent acute and chronic cholestatic liver injury.

Background

Prochlorperazine (proe" klor per' a zeen) is a tricyclic aliphatic phenothiazine which acts by postsynaptic inhibition of dopamine receptors. Prochlorperazine has other peripheral and central nervous system effects, producing both alpha adrenergic stimulation and blocking histamine- and serotonin-mediated effects. Prochlorperazine is indicated primarily for the therapy of nausea and vomiting. Prochlorperazine also has antianxiety and antipsychotic effects, but is used less commonly for these indications compared to the major phenothiazines such as chlorpromazine, fluphenazine, perphenazine, thioridazine and trifluoperazine. Prochlorperazine was approved for use in the United States in 1956 and is still widely used in therapy of nausea and vomiting. Prochlorperazine is available in generic forms as tablets of 5, 10 and 25 mg, in long acting capsules of 15 mg, as an oral solution of 5 mg/ 5 mL, as suppositories of 2.5, 5 and 25 mg, and in parenteral forms. Prochlorperazine is also available under the brand names of Compazine and Compro. Typical doses for nausea are 5 to 10 mg three to four times daily. Common side effects are similar to other phenothiazines and include drowsiness, dizziness, headache, blurred vision, dry mouth, constipation, tremor, restlessness, muscle spasms and weight gain.

Hepatotoxicity

Liver test abnormalities are uncommon during prochlorperazine therapy, perhaps because it is rarely given long term or in high doses chronically. Aminotransferase elevations can occur during therapy, but they are usually mild, asymptomatic and transient and reversible even with continuation of medication. Rare instances of clinically apparent acute liver injury have been reported due to prochlorperazine which resemble the liver injury associated with chlorpromazine. The onset of jaundice is usually within 1 to 4 weeks, and the pattern of serum enzyme elevations is typically cholestatic or mixed. Immunoallergic features (fever and eosinophilia) occur in some cases, but they are usually mild and self-limited; autoantibodies are rare. Liver biopsy typically shows a cholestatic hepatitis. Importantly, prochlorperazine jaundice can be prolonged and has been associated with rare cases of vanishing bile duct syndrome (Case 1) that can be fatal or ultimately require liver transplantation.

Mechanism of Injury

The mechanism by which prochlorperazine causes serum aminotransferase elevations is not known but is likely shared with other phenothiazines. Several features of the clinical presentation of prochlorperazine hepatotoxicity (short latency period, fever, eosinophilia) suggest a hypersensitivity reaction, and rechallenge typically causes a rapid recurrence of injury. Prochlorperazine is extensively metabolized by the liver via sulfoxidation and oxidation, and some instances of serum aminotransferase elevations as well as more clinically apparent liver injury may be caused by production of a toxic intermediate of its metabolism.

Outcome and Management

The serum aminotransferase elevations that occur on prochlorperazine therapy are usually transient and do not require dose modification or discontinuation of therapy. The acute cholestatic hepatitis caused by prochlorperazine is typically self-limited and benign but should prompt immediate discontinuation. A small proportion of cases are followed by prolonged jaundice and cholestasis and features of vanishing bile duct syndrome. Many patients with chronic cholestasis eventually improve, but they may have persistent enzyme elevations and biliary cirrhosis. Fatalities from prochlorperazine jaundice have been reported. Rechallenge with phenothiazines usually causes a prompt recurrence of the liver injury and should be avoided.

Drug Class: Gastrointestinal Agents; Antipsychotic Agents

Other Drugs in the Subclass, Antipsychotic Agents, Phenothiazines: Chlorpromazine, Fluphenazine, Perphenazine, Thioridazine, Trifluoperazine

CASE REPORT

Case 1. Prolonged cholestatic liver injury due to prochlorperazine.

(Modified from: Lok AS, Ng IO. Prochlorperazine-induced chronic cholestasis. J Hepatol 1988; 6: 369-73. PubMed Citation)

A 68 year old man was treated with trimethoprim/sulfamethoxazole (800/400 mg three times daily) for one week and prochlorperazine (10 mg daily) for 4 weeks for suspected otitis media. A few weeks after stopping prochlorperazine, he developed jaundice and pruritus. When first seen, one month after stopping medications, serum bilirubin was 18.4 mg/dL, alkaline phosphatase was 1.5 times normal and ALT was minimally elevated (Table). Tests for viral hepatitis and abdominal ultrasound were normal. After persistence of jaundice for 3 months, a liver biopsy was done which showed centrilobular cholestasis with minimal hepatocyte necrosis or portal inflammation. The intralobular bile ducts were normal. He continued to have jaundice and severe pruritus and developed skin hyperpigmentation. Tests for hepatitis B and mitochondrial antibody were negative. Endoscopic retrograde cholangiopancreatography was normal. Serum bilirubin levels peaked 4 months after presentation and then began to decline, not becoming normal until one year later. Pruritus and hyperpigmentation also resolved, but serum alkaline phosphatase and GGT levels remained elevated. A repeat liver biopsy, done two years after onset and 9 months after resolution of jaundice and symptoms, showed minimal cholestasis but bridging hepatic fibrosis and paucity of intralobular bile ducts. Two-and-a-half years after onset, serum alkaline phosphatase levels were still abnormal but he had no symptoms.

Key Points

Medication:	Prochlorperazine (10 mg daily for 4 weeks)
Pattern:	Cholestatic
Severity:	4+ (prolonged jaundice and hepatic fibrosis)

Table continued from previous page.

Latency:	3 weeks
Recovery:	Incomplete after 2 years
Other medications:	Trimethoprim/sulfamethoxazole

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Alk P* (U/L)	Bilirubin* (mg/dL)	Other
		Chlorpromazine (50 mg daily) given for nausea for 4 weeks			
1 month	0	49	116	18.4	
	3 months	80	210	26.2	Biopsy #1
	4 months	88	219	19.3	ERCP normal
	6 months	85	365	11.2	
	10 months	65	430	2.6	
1 year	12 months	60	410	1.5	
2 years	22 months	85	445	1.0	Biopsy #2
Normal Values		**<42**	**<90**	**<1.2**	

* Some values estimated from Figure 1 and bilirubin converted from μmol/L to mg/dL.

Comment

A typical example of the evolution of an acute cholestatic hepatitis to prolonged cholestasis and vanishing bile duct syndrome. The patient eventually improved and was asymptomatic, but alkaline phosphatase levels were persistently elevated and liver biopsy showed paucity of intralobular bile ducts and bridging hepatic fibrosis. Not all cases of vanishing bile duct syndrome progress to hepatic failure and eventual clinical improvement is common. Long term follow up on such cases usually demonstrates well compensated and nonprogressive cirrhosis and persistence of mild elevations in serum alkaline phosphatase.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Prochlorperazine – Generic, Compazine®, Compro®

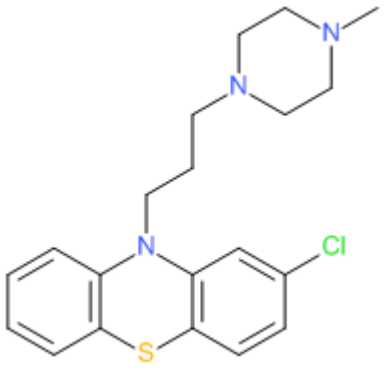
DRUG CLASS

Gastrointestinal Agents; Antipsychotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Prochlorperazine	58-38-8	C20-H24-Cl-N3-S	

ANNOTATED BIBLIOGRAPHY

References updated: 23 January 2014

Zimmerman HJ. Neuroleptic drugs. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 483-91.

(Expert review of hepatotoxicity of neuroleptic drugs including chlorpromazine published in 1999; several hundred cases of chlorpromazine jaundice have been reported, usually cholestatic, arising after 1-5 weeks, often with fever and eosinophilia, sometimes causing vanishing bile duct syndrome; other phenothiazines have only rarely been linked to liver injury, except for prochlorperazine).

Larry D, Ripault MP. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 447-62.

(Review of phenothiazine hepatotoxicity mentions that liver enzyme elevations arise in up to 40% of patients, and hundreds of cases of chlorpromazine jaundice have been published with a frequency of 0.5-1%, onset within 2-5 weeks and usually presenting with acute cholestatic hepatitis with jaundice and pruritus and a prolonged course in 7%; other phenothiazines have been linked to liver injury similar to that of chlorpromazine, "but with a lower frequency").

Meyer JM. Pharmacotherapy of psychosis and mania. In, Brunton LL, Chabner BA, Knollman BA, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 417-56.

(Textbook of pharmacology and therapeutics).

Mechanic RC, Meyers L. Chlorpromazine-type cholangitis; report of a case occurring after the administration of prochlorperazine. N Engl J Med 1958; 259: 778-80. PubMed PMID: 13590448.

(68 year old woman developed jaundice within 10 days of starting once daily prochlorperazine for nausea [peak bilirubin 26.8 mg/dL, AST 77 U/L, Alk P ~3 fold elevated], resolving slowly after stopping and undergoing laparotomy for suspected extrahepatic biliary obstruction).

Milne HB, Berliner F. A clinical trial of Stemetil(prochlorperazine). J Ment Sci 1958; 104: 873-9. PubMed PMID: 1358834.

Solomon FA Jr, Campagna FA. Jaundice due to prochlorperazine(compazine). Am J Med 1959; 27: 840-3. PubMed PMID: 13832654.

(50 year old female developed jaundice 5 days after restarting prochlorperazine for nausea [bilirubin 19.2 mg/dL, Alk P ~20 times ULN]; biopsy showed intrahepatic cholestasis similar to chlorpromazine jaundice).

Crandell A, Ma JY. Jaundice precipitated by prochlorperazine(Compazine) in the treatment of alcoholic psychiatric disturbance. J Med Soc N J 1959; 56: 553-4. PubMed PMID: 13812634.

(26 year old man with alcoholism and tuberculosis developed fever and jaundice 24 days after starting a third course of prochlorperazine; serum enzyme and bilirubin levels were not provided).

Weinstein A, Alper B, Dade J. Cholestasis due to prochlorperazine. JAMA 1959; 170: 1663-4. PubMed PMID: 13672755.

(49 year old woman developed nausea and pruritus 3 weeks after starting prochlorperazine [bilirubin 4.7 mg/dL, AST 75 U/L, Alk P ~2x ULN], biopsy showing intrahepatic cholestasis and resolving within 3-4 weeks of stopping).

Salde H, Wallindr J. [Prochlorperazine for chronic psychosis]. Svenska Lakartidningen 1961; 58: 188-97. PubMed PMID: 13745578.

(Analysis of 40 patients treated with prochlorperazine for psychosis; major side effects were sedation and extrapyramidal symptoms; no jaundice reported).

McQueen EG. Toxic effects of phenothiazine tranquillizers. N Z Med J 1963; 62: 460-2. PubMed PMID: 14073060.

(Review of the phenothiazines and their side effects; "Jaundice has occurred in about 1% of patients taking chlorpromazine, and also, although less frequently, in patients taking one of the more recently developed analogues").

McFarland RB. Fatal drug reaction associated with prochlorperazine (Compazine). Report of a case characterized by jaundice, thrombocytopenia, and agranulocytosis. Am J Clin Pathol 1963; 40: 284-90. PubMed PMID: 14063694.

(73 year old woman hospitalized for suspect myocardial infarction was given prochlorperazine and developed fever 31 days later with thrombocytopenia [bilirubin 2.8 mg/dL, AST 1480 U/L]; prochlorperazine was stopped, but she worsened and died of multiorgan failure 2 weeks later, autopsy showed centrolobular necrosis).

Cook GC, Sherlock S. Jaundice and its relation to therapeutic agents. Lancet 1965; 1: 175-9. PubMed PMID: 14238042.

(Summary of cases of drug induced liver disease seen at Royal Free Hospital between 1959-65; 11 cases of acute liver failure including 3 due to iproniazid, 2 phenelzine, 2 phenoxypropazine, 1 prochlorperazine and 3 halogenated anesthetics; 20 cases of cholestatic hepatitis including 18 due to chlorpromazine, 1 perphenazine and 1 nitrofurantoin).

Walker CO, Combes B. Biliary cirrhosis induced by chlorpromazine. Gastroenterology 1966; 51: 631-40. PubMed PMID: 5926937.

(Two patients, a 32 year old woman and a 31 year old man, developed persistent jaundice [>4 years], cholestasis and liver fibrosis 3 and 4 weeks after starting chlorpromazine; acute cholestatic hepatitis evolving into chronic form with biopsies showing cirrhosis and complications of portal hypertension).

Case records of the Massachusetts General Hospital. Case 32-1967. N Engl J Med 1967; 277: 255-62. PubMed PMID: 6029314.

(86 year old woman with complicated course after cholecystectomy resulting in multiorgan failure; autopsy showing "toxic hepatitis" and prochlorperazine considered a possible cause).

Ishak KG, Irey NS. Hepatic injury associated with the phenothiazines. Clinicopathologic and follow-up study of 36 patients. Arch Pathol 1972; 93: 283-304. PubMed PMID: 5017281.

(Review of 36 liver biopsies of phenothiazine induced hepatotoxicity from the files of the Armed Forces Institute of Pathology; 33 due to chlorpromazine, 3 prochlorperazine; mean onset 15 days, eosinophilia in 73%, mean bilirubin 12.4 mg/dL, Alk P ~8 fold elevated, ALT 146 U/L; 6 [17%] had prolonged course for 10-16 months).

Døssing M, Andreasen PB. Drug-induced liver disease in Denmark. An analysis of 572 cases of hepatotoxicity reported to the Danish Board of Adverse Reactions to Drugs. Scand J Gastroenterol 1982; 17: 205-11. PubMed PMID: 6982502.

(Among 572 cases of drug induced liver disease seen between 1968-78 in Denmark, 51 were attributed to chlorpromazine [9%, ranking 2nd behind halothane], latency averaging 14 days [range 11-46]; 5 deaths; no other phenothiazines mentioned).

Kaplowitz N, Aw TY, Simon FR, Stolz A. Drug-induced hepatotoxicity. Ann Intern Med 1986; 104: 826-39. PubMed PMID: 3518564.

(Review of drug induced hepatotoxicity including phenothiazine jaundice).

Munyon WH, Salo R, Briones DF. Cytotoxic effects of neuroleptic drugs. Psychopharmacology (Berl) 1987; 91: 182-8. PubMed PMID: 2883697.

(In vitro assay for cytotoxicity of 8 neuroleptic drugs found that chlorpromazine was more toxic than haloperidol and loxapine, but similar to other phenothiazines).

Regal RE, Bili JE, Glazer HM. Phenothiazine-induced cholestatic jaundice. Clin Pharm 1987; 6: 787-94. PubMed PMID: 2905941.

(Review of phenothiazine induced liver injury; cross sensitivity is rare "but does exist").

Lok AS, Ng IO. Prochlorperazine-induced chronic cholestasis. J Hepatol 1988; 6: 369-73. PubMed PMID: 3392386.

(68 year old man developed jaundice 4 weeks after starting prochlorperazine [peak bilirubin 26 mg/dL, ALT 50-90 U/L, Alk P 120-500 U/L], jaundice and pruritus persisting for more than a year, but then gradual clinical improvement but with persistent enzyme elevations, and biopsy 22 months after onset showed fibrosis and paucity of bile ducts: Case 1).

Bach N, Thung SN, Schaffner F, Tobias H. Exaggerated cholestasis and hepatic fibrosis following simultaneous administration of chlorpromazine and sodium valproate. Dig Dis Sci 1989; 34: 1303-7. PubMed PMID: 2502367.

(45 year old man developed fatigue and fever 12 days after starting chlorpromazine for hiccups [bilirubin 21.5 mg/dL, ALT 1312 U/L, Alk P 617 U/L], with persistent jaundice and pruritus for several years and eventual presence of cirrhosis and varices; paucity of bile ducts on biopsy).

Pillans PI. Drug associated hepatic reactions in New Zealand: 21 years experience. NZ Med J 1996; 109: 315-9. PubMed PMID: 8816722.

(Over 21 year period in New Zealand, there were 943 official reports of liver injury involving 205 drugs; chlorpromazine was in the top 20 drugs implicated accounting for 2.7% of cases; prochlorperazine was cause of 4 cases, but other phenothiazines not mentioned).

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.

(Among 126 cases of drug induced liver injury seen in Spain between 1993 and 2000, 3 were due to chlorpromazine with relative risk of 613: frequency of 261 per 100,000 person year exposures; no other phenothiazine mentioned).

Mindikoglu AL, Anantharaju A, Hartman GG, Li SD, Villanueva J, Van Thiel DH. Prochlorperazine-induced cholestasis in a patient with alpha-1 antitrypsin deficiency. Hepatogastroenterology 2003; 50: 1338-40. *(58 year old woman 9 years after lung transplant for alpha-1-antitrypsin deficiency on multiple medications including prochlorperazine for 27 months developed jaundice and chronic allograft rejection [peak* PubMed PMID: 14571732.

bilirubin 38.6 m/dL, ALT 71 U/L, Alk P 362 U/L]; drug stopped, but only 3 days of follow up provided).

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, none were due to phenothiazines).

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 including 4 due to psychotropic agents; one each for quetiapine, nefazodone, fluoxetine and venlafaxine, but none to phenothiazines).

Molleston JP, Fontana RJ, Lopez MJ, Kleiner DE, Gu J, Chalasani N; Drug-induced Liver Injury Network. Characteristics of idiosyncratic drug-induced liver injury in children: results from the DILIN prospective study. J Pediatr Gastroenterol Nutr 2011; 53: 182-9. PubMed PMID: 21788760.

(Among 30 children with suspected drug induced liver injury, half [n=15] were due to antimicrobials [minocycline 4, INH 3, azithromycin 3] and the rest largely due to CNS agents and anticonvulsants; one case was attributed to perphenazine but none to prochlorperazine).

Marwick KF, Taylor M, Walker SW. Antipsychotics and abnormal liver function tests: systematic review. Clin Neuropharmacol 2012; 35: 244-53. PubMed PMID: 22986798.

(Systematic review of the literature found rates of any serum enzyme elevation during antipsychotic therapy to range from 5-78% and "clinically significant' elevations in 0-15%; lists 12 reports of clinically apparent liver injury due to prochlorperazine, one of which was fatal [McFarland 1963]).