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Trimethobenzamide

Updated: April 10, 2014.

OVERVIEW

Introduction

Trimethobenzamide is an orally available, antiemetic agent used in the therapy of nausea and vomiting associated with medications and gastrointestinal, viral and other illnesses. Trimethobenzamide has not been linked convincingly to elevations in serum enzymes during therapy or to cases of clinically apparent liver injury with jaundice.

Background

Trimethobenzamide (trye meth" oh ben' za mide) is a benzamide used to prevent nausea and vomiting. Its mechanism of action is uncertain, but it is believed to act directly on the central chemoreceptor nausea trigger zone of the medulla oblongata of the brain. It has weak antihistaminic activity, but does not appear to act via serotonin or dopamine pathways. Trimethobenzamide was approved for use in the United States in 1974 and is widely used in therapy of nausea, vomiting caused by gastroenteritis, medications and other illnesses. Trimethobenzamide is available as 300 mg capsules in generic forms and under the brand name Tigan. It is also available as a solution for injection (100 mg/mL). Trimethobenzamide used to be available also as suppositories, but this formulation was discontinued due to lack of efficacy. The typical oral dose of trimethobenzamide for in adults is 300 mg three or four times a day as needed, usually for short periods only. Intravenous formulations are used for therapy of postoperative nausea and vomiting. Common side effects include drowsiness, dizziness, headache, fatigue, diarrhea and polyuria. Rare side effects include hypersensitivity reactions, disorientation coma and seizures.

Hepatotoxicity

Serum aminotransferase elevations during trimethobenzamide therapy are uncommon and rates of such elevations have not been reported in large clinical trials. A single case report of hepatitis and jaundice attributed to trimethobenzamide was published in 1967 that predated availability of tests for hepatitis A, B and C and of modern imaging studies. The latency to onset was approximately 2 weeks and the pattern of injury was mixed. There were no immunoallergic or autoimmune features and recovery was prompt once the medication was stopped. Since that report, there have been no publications on hepatotoxicity of trimethobenzamide despite widescale use for several decades. Trimethobenzamide is also not listed in large case series on drug induced liver injury. Thus, clinically apparent liver injury from trimethobenzamide must be very rare if it occurs at all.

Mechanism of Injury

Trimethobenzamide is metabolized in the liver but appears to have few drug-drug interactions.

Drug Class: Gastrointestinal Agents, Antiemetics

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Trimethobenzamide – Generic, Tigan®

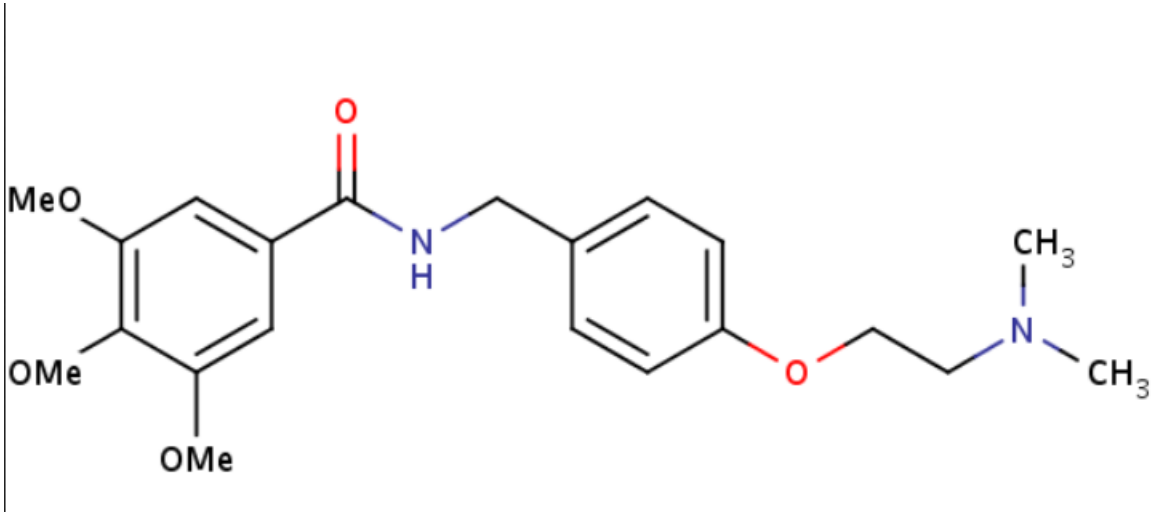
DRUG CLASS

Gastrointestinal Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Trimethobenzamide	138-56-7	C21-H28-N2-O5	

ANNOTATED BIBLIOGRAPHY

References updated: 10 April 2014

Zimmerman HJ. Antiemetic and prokinetic compounds. Miscellaneous drugs and diagnostic chemicals. In, Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999: pp. 721.

(Expert review of hepatotoxicity published in 1999 lists trimethobenzamide as having caused a single case of cholestatic liver injury [Borda and Jick: 1987]).

Sharkey KA, Wallace JL. Treatment of disorders of bowel motility and water flux: anti-emetics; agents used in biliary and pancreatic disease. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1323-50.

(Textbook of pharmacology and therapeutics).

Brandman O. Clinical evaluation of the effectiveness and safety of trimethobenzamide(tigan). Gastroenterology 1960; 38: 777-80. PubMed PMID: 13803875.

(Among 50 adults with nausea and vomiting of different causes given a single dose of trimethobenzamide [100 mg orally or intramuscularly], 84% appeared to benefit, and no adverse side effects were observed).

Wolfson B, Torres-Kay M, Foldes FF. Investigation of the usefulness of trimethobenzamide (Tigan) for the prevention of postoperative nausea and vomiting. Anesth Analg 1962; 41: 172-7. PubMed PMID: 14008063.

(Among 870 patients undergoing surgery and anesthesia treated with intramuscular trimethobenzamide vs placebo, "side effects attributable to trimethobenzamide were not observed").

Coppolino CA, Wallace G. Trimethobenzamide antiemetic in immediate postoperative period. Double-blind study in 2,000 cases. JAMA 1962; 180: 326-8. PubMed PMID: 13881235.

(Among 2000 patients scheduled for elective surgery given intramuscular injections of trimethobenzamide or placebo, nausea was less in the trimethobenzamide treated subjects; no mention of side effects).

Moertel CG, Reitemeier RJ, Gage RP. A controlled clinical evaluation of antiemetic drugs. JAMA 1963; 186: 116-8. PubMed PMID: 14056524.

(Among 300 patients with cancer receiving fluorouracil who were randomized to receive one of 6 oral antiemetic regimens, the only "significant" side effect was over sedation, which occurred in 8% given prochlorperazine but 0% on trimethobenzamide).

Nichamin SJ. Severe allergic reaction to an antiemetic trimethobenzamide hydrochloride (Tigan). Harper Hosp Bull 1964 Jan-Feb; 22: 2-5. PubMed PMID: 14103491.

(4 year old boy developed abdominal pain, arthritis and facial edema a few hours after an intramuscular injection of trimethobenzamide [8% eosinophilia, no liver tests reported], resolving within 3-4 days with epinephrine and diphenylhydramine).

Bardfeld PA. A controlled double-blind study of trimethobenzamide, prochlorperazine, and placebo. JAMA 1966; 196: 796-8. PubMed PMID: 5326281.

(Among 126 patients with nausea or vomiting of various causes treated with intramuscular injections of trimethobenzamide, prochlorperazine or placebo, drowsiness occurred in 12% and dizziness in 2% of trimethobenzamide treated patients, but no other adverse events were recorded).

Borda I, Jick H. Hepatitis following the administration of trimethobenzamide hydrochloride. Arch Intern Med 1967; 120: 3 71-3. PubMed PMID: 6038296.

(50 year old woman with breast cancer receiving irradiation therapy developed jaundice 2 weeks after starting oral trimethobenzamide for prevention of nausea [bilirubin 15.3 mg/dL, ALT 330 U/L, Alk P 14.3 Sigma units], resolving within the following month).

Hurley JD, Eshelman FN. Trimethobenzamide HCl in the treatment of nausea and vomiting associated with antineoplastic chemotherapy. J Clin Pharmacol 1980; 20: 352-6. PubMed PMID: 7400373.

(Among 55 patients receiving cancer chemotherapy given intramuscular injections of trimethobenzamide or placebo four times daily for 48 hours, "no side effects attributable to trimethobenzamide were recorded").

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, no cases were attributed to an antiemetic).

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 none were attributed to antiemetic 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.

(Among 624,673 adverse event reports in children between 2000 and 2006 in the WHO VigiBase, 1% were hepatic, but no antiemetic was listed among the 41 most commonly implicated agents).

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 attributed to antiemetics).

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, the most common implicated agents being nimesulide [n=53: 30%], cyproterone [n=18], nitrofurantoin [n=17], antituberculosis drugs [n=13] and flutamide [n=12: 7%]; no antiemetic was listed).