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Loxapine

Updated: May 21, 2019.

OVERVIEW

Introduction

Loxapine is a conventional antipsychotic used in the therapy of schizophrenia. Loxapine therapy is commonly associated with minor serum aminotransferase elevations and in very rare instances has been linked to clinically apparent acute liver injury.

Background

Loxapine (lox' a peen) is a dibenzoxazepine tricyclic derivative which appears to act by blocking dopamine type 2 (D2) receptors. Loxapine has other central and peripheral effects including anticholinergic and α-adrenergic blockade. Loxapine is indicated for the therapy of psychotic disorders and was approved for this use in the United States in 1976. In recent years, loxapine has been replaced in large part by the atypical antipsychotics, which have fewer extrapyramidal side effects. Loxapine is available as tablets of 5, 10, 25 and 50 mg and in generic forms and previously under the brand name Loxitane. Recommended doses of oral loxapine are 10 mg twice daily initially, increasing to a maximum of 100 mg in divided doses daily. An aerosol formulation of loxapine has recently been developed (Adasuve) that is recommended for use in acute agitation in patients with bipolar disorder or schizophrenia. Common side effects include drowsiness, dizziness, headache, blurred vision, dry mouth, and tremor. Loxapine, unlike many antipsychotic agents, is not associated with significant weight gain. Rare, potentially severe adverse events of first generation antipsychotic agents may include increased mortality in elderly patients with dementia-related psychosis, tardive dyskinesia, neuroleptic malignant syndrome, orthostatic hypotension, falls and agranulocytosis.

Hepatotoxicity

Liver test abnormalities have been reported to occur in a small proportion of patients on long term therapy with loxapine, but elevations are uncommonly above 3 times the upper limit of normal. The aminotransferase abnormalities are usually mild, asymptomatic and transient, reversing even with continuation of medication. Instances of clinically apparent acute liver injury have been reported due to loxapine and to the structurally related tricylic amoxapine (not available in the United States), but cases are rare. In reported cases, the onset of jaundice was within 4 to 8 weeks, and the pattern of serum enzyme elevations was typically hepatocellular. Immunoallergic features and autoantibody formation were not prominent. All cases were self-limited without fatalities or residual chronic liver injury.

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

Mechanism of Injury

The mechanism by which loxapine causes serum aminotransferase elevations is not known, but is likely due to production of a toxic intermediate by its metabolism. Loxapine is extensively metabolized by the liver via sulfoxidation and oxidation, partially via P450 system.

Outcome and Management

The serum aminotransferase elevations that occur on loxapine therapy are usually self-limited and do not require dose modification or discontinuation of therapy. No instances of acute liver failure or vanishing bile duct syndrome due to loxapine have been reported. Patients with loxapine induced liver injury probably do not have cross sensitivity to atypical antipsychotics.

Drug Class: Antipsychotic Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Loxapine – Generic, Loxitane®

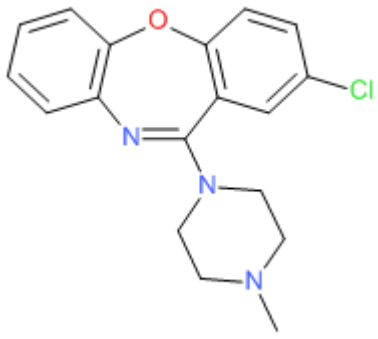
DRUG CLASS

Antipsychotic Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Loxapine	1977-10-2	C18-H18-Cl-N3-O	

ANNOTATED BIBLIOGRAPHY

References updated: 21 May 2019

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 loxapine published in 1999, mentions that loxapine has been incriminated in cases of hepatic injury reported to the FDA, onset within first 3 weeks).

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. 443-62.

(Review of hepatotoxicity of psychiatric agents; loxapine "..has been implicated in one case of hepatocellular injury...").

Meyer JM. Pharmacotherapy of psychosis and mania. 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. 279-302.

(Textbook of pharmacology and therapeutics).

Clark ML, Huber WK, Sullivan J, Wood F, Costiloe JP. Evaluation of loxapine succinate in chronic schizophrenia. Dis Nerv Syst 1972; 33: 783-91. PubMed PMID: 4589978.

(Controlled trial comparing placebo, loxapine and chlorpromazine in 55 inpatients with schizophrenia; elevations in AST and Alk P occurred no more frequently with loxapine than placebo).

Heel RC, Brogden RN, Speight TM, Avery GS. Loxapine: a review of its pharmacological properties and therapeutic efficacy as an antipsychotic agent. Drugs 1978; 15: 198-217. PubMed PMID: 25167.

(Review of structure, pharmacology, mechanism of action, efficacy and safety of loxapine; "Transient… abnormalities in liver function test values have been observed in a few patients, but did not appear to be clinically significant").

Reynolds PC, Som CW, Herrmann PW. Loxapine fatalities. Clin Toxicol 1979; 14: 181-5. PubMed PMID: 436393.

(Two cases of suicidal overdose [2.5-2.9 grams] marked by coma, seizures and cardiovascular collapse within hours to days).

Tam CW, Olin BR 3rd, Ruiz AE. Loxapine-associated rhabdomyolysis and acute renal failure. Arch Intern Med 1980; 140: 975-6. PubMed PMID: 6770772.

(22 year old man with suicidal loxapine overdose [~4 grams] developed rhabdomyolysis and acute renal failure; CPK 15,000 U/L and AST 54 U/L, but normal bilirubin and alkaline phosphatase).

DePaulo JR Jr, Ayd FJ Jr. Loxapine: fifteen years' clinical experience. Psychosomatics 1982; 23: 261-71. PubMed PMID: 7041162.

("Hepatic… adverse effects with loxapine are extremely rare, but transitory fluctuations in…liver enzyme levels have occasionally been noted in clinical studies").

Patterson JP. Amoxapine associated with hepatotoxicity. J Clin Psychopharmacol 1987; 7: 50-1. PubMed PMID: 3818992.

(38 year old man developed serum enzyme elevations 2 days after starting amoxapine which was continued for 24 days with enzymes rising to 30 days with tender liver, falling to normal thereafter; no specifics given).

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

(In vitro testing for cytotoxicity found the phenothiazines to be the most, haloperidol intermediate and loxapine and molindone least toxic).

Manapany M, Marchetti B, Bertrand-Lepensec D, Lacroix G, Legré M. [Acute cytolytic hepatitis caused by amoxapine]. Gastroenterol Clin Biol 1993; 17: 405-6. PubMed PMID: 8349085.

(29 year old woman developed nausea and abdominal pain 18 days after starting amoxapine [bilirubin normal, ALT 736 U/L, Alk P 295 U/L], resolving within a month of stopping).

Allison DB, Mentore JL, Heo M, Chandler LP, Cappelleri JC, Infante MC, Weiden PJ. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999; 156: 1686-96. PubMed PMID: 10553730.

(Systematic review of 81 articles on weight change with antipsychotics, using change after 10 weeks to compare agents: clozapine +5.7, olanzapine +4.2, chlorpromazine +4.2, quetiapine +2.5, risperidone +1.7, loxapine +0.6, haloperidol +0.5, ziprasidone +0.3, molindone -0.1, and pimozide -2.7 kg).

Chakrabarti A, Bagnall A, Chue P, Fenton M, Palaniswamy V, Wong W, Xia J. Loxapine for schizophrenia. Cochrane Database Syst Rev 2007; (4): CD001943. PubMed PMID: 17943763.

(Cochrane review of efficacy and safety of loxapine; no mention of ALT elevations or hepatic side effects).

Torrent C, Amann B, Sanchez-Moreno J, Colom F, Feinares M, Comes M, Rosa AR, et al. Weight gain in bipolar disorder: pharmacological treatment as a contributing factor. Acta Psychiatr Scand 2008; 118: 4-18. PubMed PMID: 18498432.

(Review of frequency of weight gain in patients treated for bipolar disorders, most weight gain occurred with clozapine and olanzapine, but some weight gain also with quetiapine, risperidone, lithium, valproate and gabapentin; little or none with molindone, loxapine, carbamazepine and lamotrigine).

Allen MH, Feifel D, Lesem MD, Zimbroff DL, Ross R, Munzar P, Spyker DA, et al. Efficacy and safety of loxapine for inhalation in the treatment of agitation in patients with schizophrenia: a randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2011; 72: 1313-21. PubMed PMID: 21294997.

(Controlled trial of inhaled loxapine in 129 patients with acute agitation and schizophrenia; side effects included dysgeusia, dizziness, and local irritation; no mention of hepatotoxicity).

Kwentus J, Riesenberg RA, Marandi M, Manning RA, Allen MH, Fishman RS, Spyker DA, et al. Rapid acute treatment of agitation in patients with bipolar I disorder: a multicenter, randomized, placebo-controlled clinical trial with inhaled loxapine. Bipolar Disord 2012; 14: 31-40. PubMed PMID: 22329470.

(Controlled trial of inhaled loxapine 314 patients with acute agitation and bipolar disorder; no serious adverse events or mention of liver injury).

Currier G, Walsh P. Safety and efficacy review of inhaled loxapine for treatment of agitation. Clin Schizophr Relat Psychoses 2013; 7: 25-32. PubMed PMID: 23538290.

(Review of the safety and efficacy of inhaled loxapine).

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, but none were attributed to loxapine or other antipsychotic medications).

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, five were attributed to atypical antipsychotics [3 quetiapine, 2 olanzapine], but none to loxapine).

Drugs for psychotic disorders. Med Lett Drugs Ther 2016; 58 (1510): 160-4. PubMed PMID: 27960194.

(Concise review of medications available in the US for therapy of psychotic disorders; mentions that loxapine is a first generation agent and generically available, but does not discuss loxapine individually or mention ALT elevations or hepatotoxicity for any of the agents discussed)