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Amoxapine

Updated: March 2, 2016.

OVERVIEW

Introduction

Amoxapine is a tetracyclic antidepressant used for relief of symptoms of depression caused by either reactive or psychotic depression. Amoxapine has been associated with a low rate of minor serum aminotransferase elevations during treatment and to very rare instances of clinically apparent acute liver injury.

Background

Amoxapine (a mox' a peen) is a tetracyclic antidepressant belonging to the dibenzoxapine family, similar but somewhat distinct from classical tricyclic antidepressants. Amoxapine has been shown to be effective in both reactive and neurotic depression as well as in major, endogenous depressive disorders. As with other tricyclic antidepressants, the mechanism of action of amoxapine probably involves interruption of norepinephrine transmission. Amoxapine also blocks histaminic and cholinergic receptors which account for its mild sedative effects. Amoxapine was approved for use in the United States in 1992 and is available in tablets of 25, 50, 100 and 150 mg generically and previously under the brand name Ascendin. Recommended doses are 50 mg two or three times daily initially, increasing based upon efficacy and tolerance and changing to once daily dosing, to as high as 300 mg once daily. Common side effects included drowsiness, dizziness, headache, blurred vision, dry mouth, and tremor. Less common and rare side effects include extrapyramidal signs and symptoms, tardive dyskinesia, suicidal ideation, heart arrhythmias and galactorrhea.

Hepatotoxicity

Liver test abnormalities occur in a small proportion of patients on long term therapy with amoxapine, but elevations are usually mild, asymptomatic and transient, reversing even with continuation of medication. Instances of clinically apparent acute liver injury without jaundice have been reported due to amoxapine, but have been quite rare. Published cases have been mild, anicteric and asymptomatic. The onset of injury was within 1 to 4 weeks of starting, and the pattern of serum enzyme elevations was hepatocellular. Immunoallergic features and autoantibody formation were not present.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which amoxapine causes serum aminotransferase elevations is not known, but is likely due to production of a toxic intermediate by its metabolism. Amoxapine is metabolized by the liver via the P450 system (predominantly CYP 2D6).

Outcome and Management

The serum aminotransferase elevations that occur on amoxapine 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 amoxapine have been reported. There is no information on cross sensitivity to liver injury between amoxapine and other tricyclic antidepressants, but switching to another class of agents (such as the selective serotonin reuptake inhibitors) is probably prudent.

Drug Class: Antidepressant Agents

Other Drugs in the Subclass, Tricyclics: Amitriptyline, Clomipramine, Desipramine, Doxepin, Imipramine, Nortriptyline, Protriptyline, Trimipramine

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Amoxapine – Generic, Asendin®

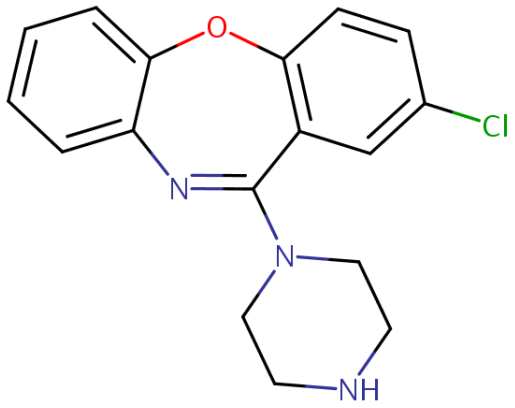
DRUG CLASS

Antidepressant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Amoxapine	14028-44-5	C17-H16-Cl-N3-O	

ANNOTATED BIBLIOGRAPHY

References updated: 02 March 2016

Zimmerman HJ. Tricyclic antidepressants. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 495-8.

(Expert review of hepatotoxicity published in 1999; amoxapine is listed as a tricyclic antidepressant with a very low rate of hepatotoxicity).

Larrey 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 antidepressant hepatotoxicity; amoxapine is listed as a tricyclic antidepressant associated with rare hepatocellular injury and latency of 4-18 days).

O'Donnell JM, Shelton RC. Drug therapy of depression and anxiety disorders. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman.s the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 397-416.

(Textbook of pharmacology and therapeutics).

Takahashi R, Sakuma A, Hara T, Kazamatsuri H, Mori A, Saito Y, Murasaki M, et al. Comparison of efficacy of amoxapine and imipramine in a multi-clinic double-blind study using the WHO schedule for a standard assessment of patients with depressive disorders. J Int Med Res 1979; 7: 7-18. PubMed PMID: 369926.

(Among 122 Japanese patients with depression treated with amoxapine or imipramine for 3-5 weeks, "abnormal laboratory data indicating any serious dysfunction of internal organs were not observed").

Rickels K, Case WG, Werblowsky J, Csanalosi I, Schless A, Weise CC. Amoxapine and imipramine in the treatment of depressed outpatients: a controlled study. Am J Psychiatry 1981; 138: 20-4. PubMed PMID: 7446776.

(Among 158 patients with depression treated with amoxapine, imipramine or placebo for 6 weeks, common side effects were sedation, agitation and dry mouth; no mention of ALT abnormalities or hepatotoxicity).

Jue SG, Dawson GW, Brogden RN. Amoxapine: a review of its pharmacology and efficacy in depressed states. Drugs 1982; 24: 1-23. PubMed PMID: 7049659.

(Review of amoxapine safety and efficacy mentions that side effects are generally mild and include anticholinergic effects and rare instances of extrapyramidal side effects and galactorrhea).

Ban TA, Fujimori M, Petrie WM, Ragheb M, Wilson WH. Systematic studies with amoxapine, a new antidepressant. Int Pharmacopsychiatry 1982; 17: 18-27. PubMed PMID: 7045016.

(Review of 2 studies of amoxapine comparing once to twice daily dosing suggested that once daily regimens are appropriate for maintenance therapy; no mention of ALT elevations or hepatotoxicity).

Litovitz TL, Troutman WG. Amoxapine overdose. Seizures and fatalities. JAMA 1983; 250: 1069-71. PubMed PMID: 6876345.

(Review of cyclic antidepressant overdoses reported to two local poison centers during an 18 month period identified 33 due to amoxapine, 27 suicidal and 4 accidental [pediatric], included 3 who were asymptomatic, 10 with mild drowsiness, 15 with severe toxicity [seizures, coma, tachycardia], and 5 fatalities [hyperthermia and persistent seizures]; no mention of liver test abnormalities or hepatic manifestations).

Winek CL, Wahba WW, Rozin L. Amoxapine fatalities: three case studies. Forensic Sci Int 1984; 26: 33-8. PubMed PMID: 6510852.

(Three cases of fatal suicidal overdoses with amoxapine, one patient presenting with stupor and seizures followed by cardiac arrest; no mention of liver abnormalities).

Gelenberg AJ, Wojcik JD, Lydiard RB, McCormick MG, Falk WE, Hicks RH, Curren FC, Cohen BM. Double-blind comparison of amoxapine and imipramine in the treatment of depressed patients. J Clin Psychiatry 1984; 45: 54-56, 57-9. PubMed PMID: 6363397.

(In a trial comparing amoxapine with imipramine in 69 patients with major depression, efficacy and safety were similar and side effects were largely due to anticholinergic effects; no mention of ALT elevations or hepatotoxicity).

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

(33 year old man with depression developed elevated liver tests within 4 days of starting amoxapine which worsened for the next 20 days until the drug was stopped, falling to normal within 2 weeks; no specific enzyme or bilirubin results given).

Leonard BE. Safety of amoxapine. Lancet 1989; 2 (8666): 808. PubMed PMID: 2571052.

(Letter stressing the neurologic side effects of amoxapine when compared to the tricyclic antidepressants; no mention of liver injury).

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

(29 year old woman developed nausea and fatigue 18 days after starting amoxapine [bilirubin normal, peak ALT 838 U/L, Alk P 295 U/L], resolving within a month of stopping).

Lucena M, Carvajal A, Andrade R, Velasco A. Antidepressant-induced hepatotoxicity. Expert Opin Drug Saf 2003; 2: 249-62. PubMed PMID: 12904104.

(Review of hepatotoxicity of antidepressants mentions two case reports of cytolytic hepatitis attributed to amoxapine [Patterson 1987, Manapany 1993]).

Degner D, Grohmann R, Kropp S, RüE, Bender S, Engel RR, Schmidt LG. Severe adverse drug reactions of antidepressants: results of the German multicenter drug surveillance program AMSP. Pharmacopsychiatry 2004; 37 Suppl 1: S39-45. PubMed PMID: 15052513.

(53,042 patients treated with antidepressants in 35 psychiatric hospitals in Germany from 1993-2000 were monitored for adverse drug reactions; increased liver enzymes reported in 16% on tricyclics, 5.5% on SSRIs and 12% of monoamine oxidase inhibitors; amoxapine not specifically mentioned or discussed).

Kudo K, Inoue H, Ishida T, Tsuji A, Ikeda N. A fatal case of amoxapine poisoning under the influence of chronic use of psychotropic drugs. Leg Med(Tokyo) 2007; 9: 63-7. PubMed PMID: 17150394.

(43 year old woman found dead with high serum levels of amoxapine, autopsy showing no liver abnormalities).

DeSanty KP, Amabile CM. Antidepressant-induced liver injury. Ann Pharmacother 2007; 41: 1201-11. PubMed PMID: 17609231.

(Review of drug induced liver injury and summary analysis of reports of injury from MAO inhibitors, SSRIs, tricyclics and atypical agents; amoxapine is not specifically discussed).

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: 20949331.

(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 [quetiapine, nefazodone, fluoxetine and venlafaxine], but none were linked to amoxapine).

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, one was attributed to venlafaxine [an SSRI], but none to amoxapine or other tricyclic antidepressants).

Park SH, Ishino R. Liver injury associated with antidepressants. Curr Drug Saf 2013; 8: 207-23. PubMed PMID: 23914755.

(Review of drug induced liver injury due to antidepressants; amoxapine is not discussed).

Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry 2014; 171: 404-15. PubMed PMID: 24362450.

(Review of the frequency and clinical features of drug induced liver injury due to antidepressants; imipramine, desipramine and amitriptyline are discussed, but not amoxapine).

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, one of which was attributed to amitriptyline, but none to amoxapine or other tricyclic antidepressants).

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, 20 cases were attributed to antidepressants including one tricyclic [imipramine], but none were attributed to amoxapine).