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Citalopram

Updated: October 12, 2017.

OVERVIEW

Introduction

Citalopram and escitalopram are selective serotonin reuptake inhibitors (SSRIs) and widely used antidepressants. Citalopram is a racemic mixture, whereas escitalopram is its S-enantiomer. Both agents have similar profiles of clinical efficacy and side effects. Both have been associated with rare instances of clinically apparent acute liver injury.

Background

Citalopram (sye tal' o pram) and escitalopram (es" sye tal' oh pram) are antidepressants that belong to the class of selective serotonin reuptake inhibitors (SSRIs). By blocking the reuptake of serotonin in CNS synaptic clefts, SSRIs increase serotonin levels and serotonin activity which results in antidepressant effects. Citalopram was approved for use in the United States in 1998 and it has become one of the most widely used antidepressant medications, with more than 16 million prescriptions being written yearly. Citalopram is available as tablets of 10, 20 and 40 mg and in an oral solution of 10 mg/5 mL in several generic forms and under the brand name of Celexa. The recommended dosage of citalopram in adults is 20 mg once daily, increasing to 40 mg daily if necessary. Escitalopram was approved for use in the United States in 2002 and is available in tablets of 5, 10, and 20 mg under the brand name Lexapro. The recommended dosage of escitalopram is 10 mg once daily, increasing to 20 mg daily if necessary. Both citalopram and escitalopram are approved for treatment of major depression; escitalopram is also used for generalized anxiety disorder. Side effects of citalopram and escitalopram are similar; common side effects are drowsiness, dyspepsia, nausea, headache, increased sweating and sexual dysfunction. Rare, but potentially severe adverse events include suicidal ideation and behavior, prolongation of the QTc interval, serotonin syndrome, precipitation of acute mania and acute glaucoma.

Hepatotoxicity

Liver test abnormalities have been reported to occur in less than 1% of patients on citalopram, and elevations are usually modest and rarely require dose modification or discontinuation. Rare instances of acute, clinically apparent episodes of liver injury with marked liver enzyme elevations with or without jaundice have been reported in patients on citalopram and escitalopram. The typical presentation is with fatigue, nausea and abdominal pain 2 to 10 weeks after starting the medication, followed by dark urine and mild jaundice. Both cholestatic and hepatocellular patterns of serum enzyme elevations have been described. Autoimmune (autoantibodies) and immunoallergic features (rash, fever, eosinophilia) are uncommon. Recovery is usually rapid once the agent is stopped.

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

Mechanism of Injury

The mechanism by which citalopram and escitalopram cause liver injury is not known. Citalopram and escitalopram are extensively metabolized by the liver, mainly via the cytochrome P450 system (CYP 3A4, 2D6 and 2C19) and hepatotoxicity may be mediated by toxic intermediates of their metabolism.

Outcome and Management

The serum aminotransferase elevations that occur on citalopram therapy are usually self-limited and do not require dose modification or discontinuation of therapy. No instances of acute liver failure or chronic vanishing bile duct syndrome have been attributed to citalopram or escitalopram. Persons with intolerance to citalopram may have similar reactions to other SSRIs and careful monitoring is warranted if other such agents are used.

Drug Class: Antidepressant Agents

Other Drugs in the Subclass, SNRIs/SSRIs: Duloxetine, Fluoxetine, Fluvoxamine, Levomilnacipran, Paroxetine, Sertraline, Venlafaxine, Vilazodone, Vortioxetine

CASE REPORT

Case 1. Acute cholestatic liver injury due to citalopram.

[Modified from: Milkiewicz P, Chilton AP, Hubscher SG, Elias E. Antidepressant induced cholestasis: hepatocellular redistribution of multidrug resistant protein (MRP2). Gut 2003; 52: 300-3. PubMed Citation]

A 30 year old woman developed jaundice and pruritus 2 months after starting citalopram for depression (10 mg daily for 1 month, followed by 20 mg daily). She had chronic depression and had been treated in the past with fluoxetine for a year without complications, but with inadequate control of her symptoms. She was taking no other medications. She had a history of cholestasis managed with ursodiol during two pregnancies. Blood tests showed a bilirubin of 4.4 mg/dL and prominent elevations in alkaline phosphatase, with minimal increase in aminotransferase levels (Table). Tests for hepatitis A, B and C and for autoimmune liver disease were negative. An abdominal ultrasound showed no evidence of biliary obstruction. A liver biopsy showed intrahepatic cholestasis without bile duct loss, fat or fibrosis. Citalopram was stopped and her jaundice and pruritus resolved over the next two months. When seen 6 months after stopping citalopram, she was asymptomatic of liver disease and serum enzymes were normal.

Key Points

Medication:	Citalopram (20 mg daily)
Pattern:	Cholestatic (R=~0.6)
Severity:	3+ (jaundice, hospitalization)
Latency:	2 months
Recovery:	2-3 months
Other medications:	None

Laboratory Values

Time After Starting	Time After Stopping	AST (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
8 weeks	0	33	637	4.4	Citalopram stopped
12 weeks	4 weeks		610	2.5	Estimated from Figure 1

Table continued from previous page.

Time After Starting	Time After Stopping	AST (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
32 weeks	24 weeks	13	277	0.4	
Normal Values		**<35**	**<360**	**<1.2**	

Comment

The abrupt onset of jaundice and pruritus suggests a cholestatic form of drug induced liver disease, which was confirmed in this case by both the pattern of serum enzyme elevations (an R value of less than 2.0) and liver histology. While usually benign, cholestatic hepatitis from medications can be prolonged. The liver biopsy showing a lack of bile duct loss and the history of cholestasis of pregnancy suggest that interference with bile secretion rather than frank injury to bile ducts was the cause.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Citalopram – Celexa®

Escitalopram – Lexapro®

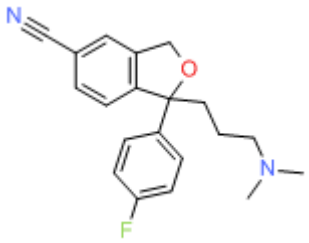
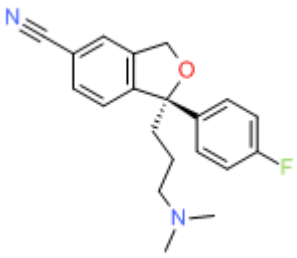
DRUG CLASS

Antidepressant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Citalopram	59729-33-8	C20-H21-F-N2-O	
Escitalopram	128196-01-0	C20-H21-F-N2-O	

ANNOTATED BIBLIOGRAPHY

References updated: 12 October 2017

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 hepatotoxicity of antidepressants mentions that clinically apparent liver injury from the SSRIs is rare and citalopram has been implicated in only a few isolated cases).

O'Donnell JM, Shelton RC. Pharmacotherapy 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).

Mourilhe P, Stokes PE. Risks and benefits of selective serotonin reuptake inhibitors in the treatment of depression. Drug Saf 1998; 18: 57-82. PubMed PMID: 9466088.

(Review of pharmacology, efficacy and safety of SSRIs; no mention of ALT elevations or hepatotoxicity).

Carvajal García-Pando A, García del Pozo J, Sánchez AS, Velasco MA, Rueda de Castro AM, Lucena MI. Hepatotoxicity associated with the new antidepressants. J Clin Psychiatry 2002; 63: 135-7. PubMed PMID: 11874214.

(Analysis of cases of hepatotoxicity from antidepressants in Spanish Pharmacovigilance System from 1989-1999, identified 99 cases; among SSRIs, 26 due to fluoxetine, 14 paroxetine, 6 fluvoxamine, 5 sertraline, 3 venlafaxine and 2 citalopram; among tricyclics, 16 clomipramine 7 amitriptyline, 6 imipramine; among miscellaneous, 3 nefazodone and 1 trazodone; but all had similar rates of liver injury ranging from 1 to 3 per 100,000 patient-years of exposure, except for nefazodone at 29 per 100,000 patient-years).

Gleason OC, Yates WR, Isbell MD, Philipsen MA. An open-label trial of citalopram for major depression in patients with hepatitis C. J Clin Psychiatry 2002; 63: 194-8. PubMed PMID: 11926717.

(A pilot study in 15 patients given citalopram for depression during interferon therapy of chronic hepatitis C; average serum ALT and AST levels did not change).

Burke WJ. Escitalopram. Expert Opinion Investig Drugs 2002; 11: 1477-86. PubMed PMID: 12387707.

(Review of structure, pharmacokinetics, metabolism, efficacy and side effects of escitalopram, the S-enantiomer of citalopram; no mention of hepatotoxicity or ALT elevations on therapy).

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; antidepressant use has increased markedly between 1992 and 2002, accounting for 5% of cases of hepatotoxicity; SSRIs are less likely to cause injury than tricyclics and MAO inhibitors; range of presentations, typically self-limited and rapid recovery; no hallmarks of hypersensitivity).

Milkiewicz P, Chilton AP, Hubscher SG, Elias E. Antidepressant induced cholestasis: hepatocellular redistribution of multidrug resistant protein (MRP2). Gut 2003; 52: 300-3. PubMed PMID: 12524417.

(Two cases of cholestasis due to SSRIs; 30 year old woman with jaundice 8 weeks after starting citalopram [bilirubin 4.4 mg/dL, AST 33, Alk P 637 U/L], resolving within 2 months of stopping [Case 1]; second case was due to paroxetine).

Spigset O, Hägg S, Bate A. Hepatic injury and pancreatitis during treatment with serotonin reuptake inhibitors: data from the World Health Organization (WHO) database of adverse drug reactions. Int Clin Psychopharmacol 2003; 18:157-61. PubMed PMID: 12702895.

(Among 27,542 reports of hepatic injury in WHO database, 786 related to SSRIs [3%], including citalopram 42, fluoxetine 222, fluvoxamine 54, paroxetine 191, sertraline 112, nefazodone 91 and venlafaxine 74; only nefazodone has an excess of hepatic reports in relationship to total reports).

Degner D, Grohmann R, Kropp S, Rüther E, 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.

(Analysis of adverse drug reactions reported from 1993-2000 in 35 psychiatric hospitals; 0.7% of SSRI recipients had a severe adverse event which were hepatic in 0.05%).

Lopez-Torres E, Lucena MI, Seoane J, Verge C, Andrade RJ. Hepatotoxicity related to citalopram. Am J Psychiatry 2004; 161: 923-4. PubMed PMID: 15121663.

(44 year old man developed fatigue 8 weeks after starting citalopram and clonazepam [bilirubin normal, ALT 1078 U/L, Alk P normal], no rash or fever, resolving within 2 months of stopping citalopram while continuing other agents).

Solomons K, Gooch S, Wong A. Toxicity with selective serotonin reuptake inhibitors. Am J Psychiatry 2005; 162: 1225. PubMed PMID: 15930079.

(38 year old with abdominal pain and ALT elevations [378 U/L] without jaundice 9 days after starting fluvoxamine; positive rechallenge and recurrence with citalopram [ALT rising to 379 U/L within 4 days] and positive rechallenge with citalopram again 1 year later).

Rao N. The clinical pharmacokinetics of escitalopram. Clin Pharmacokinet 2007; 46: 281-90. PubMed PMID: 17375980.

(Review of pharmacokinetics of escitalopram; few drug-drug interactions despite P450 metabolism)

del Val Antonana A, Ortiz Polo I, Rosello Sastre E, Moreno-Osset E. Hepatitis toxica por escitalopram [Toxic hepatitis due to escitalopram]. Med Clin (Barc) 2008; 131: 796-9. PubMed PMID: 19094887.

(49 year old woman developed fatigue, dark urine, jaundice and itching 7 weeks after starting escitalopram [bilirubin 6.1 mg/dL, ALT 2400 U/L, Alk P 116 U/L], fluctuating course and slow recovery within 20 weeks of stopping).

Neumann H, Csepregi A, Evert M, Malfertheiner P. Drug-induced liver disease related to citalopram. J Clin Psychopharmacol 2008; 28: 254-5. PubMed PMID: 18344747.

(Onset of fatigue and jaundice after 3 weeks of citalopram with bilirubin 11.0 mg/dL, ALT 851 U/L, Alk P not available, resolution in 3 months).

Jimmink A, Caminada K, Hunfeld NG, Touw DJ. Clinical toxicology of citalopram after acute intoxication with the sole drug or in combination with other drugs: overview of 26 cases. Ther Drug Monit 2008; 30: 365-71. PubMed Citation

(Summary of 26 cases of citalopram overdose [often with other agents] from the Netherlands between 1997 and 2006; primarily caused tachycardia and decrease in consciousness with no evidence of liver injury).

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 from 2004 to 2008, 6 cases were attributed to duloxetine, 3 to atomoxetine, 2 to fluoxetine, 2 to bupropion, and 1 to sertraline but none to citalopram or escitalopram).

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 1 to venlafaxine and 1 to fluoxetine, but none to citalopram).

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 amitriptyline, but no other antidepressant was listed).

Merino MI, Carrero AA, García JF, Martínez JA. [Citalopram hepatotoxicity]. Med Clin (Barc) 2011; 136: 270-1. Spanish. PubMed PMID: 20206946.

(83 year old man with multiple medical problems developed marked liver enzyme elevations 4 days after starting citalopram [bilirubin not mentioned, ALT 1155 U/L, Alk P 222 U/L, LDH 2324 U/L, creatinine 2.7 mg/dL], resolving within 5 days of stopping).

Tomlin A, Reith D, Dovey S, Tilyard M. Methods for retrospective detection of drug safety signals and adverse events in electronic general practice records. Drug Saf 2012; 35: 733-43. *(Analysis of a large health care database from New Zealand identified 701 adverse events in 473 of 5612 patients [8.4%] prescribed citalopram).* PubMed PMID: 22861670.

Kwon H, Lee SH, Kim SE, Lee JH, Jee YK, Kang HR, Park BJ, et al. Spontaneously reported hepatic adverse drug events in Korea: multicenter study. J Korean Med Sci 2012; 27: 268-73. PubMed PMID: 22379337.

(Summary of 2 years of adverse event reporting in Korea; of 9360 reports, 567 were liver related, but none were attributed to antidepressants).

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

(Review of the commonly used antidepressants and their potential for causing liver injury including summary of 5 cases attributed to citalopram, onset after 4 days to 8 weeks and all resolving without residual injury).

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 citalopram or other SSRIs).

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 hepatotoxicity of antidepressants, mentions 4 case reports of injury from citalopram [n=3] and escitopram [n=1] with latency of 4 days to 8 weeks, hepatocellular injury and recovery in all).

Ferrajolo C, Coloma PM, Verhamme KM, Schuemie MJ, de Bie S, Gini R, Herings R, et al.; EU-ADR consortium. Signal detection of potentially drug-induced acute liver injury in children using a multi-country healthcare database network. Drug Saf 2014; 37: 99-108. PubMed PMID: 24446276.

(Analyses of large spontaneous reporting adverse event databases from 3 countries between 1995 and 2010 identified 125 drugs with at least one exposed case of unexplained acute liver injury in children, 20 of which had a significant association, one of the 20 being citalopram [3 cases]).

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 Citation

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 20 cases [2%] were attributed to antidepressants including 5 due to SSRIs, 3 of which were due to escitalopram).

Friedrich ME, Akimova E, Huf W, Konstantinidis A, Papageorgiou K, Winkler D, Toto S, et al. Drug-induced liver injury during antidepressant treatment: results of AMSP, a drug surveillance program. Int J Neuropsychopharmacol 2016; 19. pii: pyv126. PubMed Citation

(Among 184,234 psychiatric inpatients from 80 hospitals, 149 cases [0.08%] of drug induced liver injury were reported, with very low rates reported for escitalopram [0.01%: 2 of 18,549] and citalopram [0.02%: 4 of 20,476]).

Gollapudy S, Cronin DC, Pagel PS, Boettcher BT. Serotonin syndrome resulting from acute decompensation of nonalcoholic steatohepatitis cirrhosis in a patient chronically treated with citalopram and tramadol. J Cardiothorac Vasc Anesth 2017; 31: 1385-88. PubMed Citation

(57 year old woman with cirrhosis developed diarrhea and akathisia thought to be due to hepatic encephalopathy, but worsening with use of linezolid and fluconazole, not improving until citalopram and tramadol were discontinued suggesting acute serotonin syndrome).

Ferrajolo C, Scavone C, Donati M, Bortolami O, Stoppa G, Motola D, Vannacci A, et al.; DILI-IT Study Group. Antidepressant-induced acute liver injury: a case-control study in an Italian inpatient population. Drug Saf 2018; 41: 95-102. PubMed Citation

(Among 179 cases of hospitalizations for unexplained acute liver injury enrolled in an prospective study between 2010 and 2014, 17 had been exposed to antidepressants including 4 who received citalopram [bilirubin 0.4-0.9 mg/dL, ALT 207- 2938 U/L, Alk P 176-188 U/L], outcomes not provided).