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Paroxetine

Updated: January 10, 2014.

OVERVIEW

Introduction

Paroxetine is a selective serotonin reuptake inhibitor (SSRI) used in the therapy of depression, anxiety disorders and obsessive-compulsive disorder. Paroxetine therapy can be associated with transient asymptomatic elevations in serum aminotransferase levels and has been linked to rare instances of clinically apparent acute liver injury.

Background

Paroxetine (pa rox' e teen) is a selective serotonin reuptake inhibitor (SSRI) that acts by blocking the reuptake of serotonin in CNS synaptic clefts, thus increasing serotonin levels in the brain which is associated with its psychiatric effects. Paroxetine was approved for use in the United States in 1992 and it remains in wide use, with more than 15 million prescriptions being filled yearly. Indications for paroxetine include major depression, obsessive-compulsive disorder, panic disorder, and anxiety disorders including social anxiety, post-trauma stress and generalized anxiety disorder. Paroxetine is also used for headache, premenstrual dysphoric disorder, diabetic neuropathy and premature ejaculation. Paroxetine is available as tablets of 10, 20, 30 and 40 mg and as an oral suspension in generic forms and under the brand names of Paxil and Pexeva. The recommended dosage for depression in adults is 20 mg once daily, increasing the dosage by 10 mg increments weekly to a maximum of 50 mg. Controlled release tablets are also available that have slightly different dosing recommendations. Common side effects are drowsiness, dyspepsia, nausea, headache, increased sweating, increased appetite, weight gain and sexual dysfunction.

Hepatotoxicity

Liver test abnormalities have been reported to occur in up to 1% of patients on paroxetine, but elevations are usually modest and usually do not 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 paroxetine. The onset of injury is usually within 2 to 16 weeks, but can be more delayed, to up to 1 year. The pattern of serum enzyme elevations varies from hepatocellular to mixed or cholestatic. While most cases are mild-to-moderate in severity, severe cases with hepatic failure have been reported. Autoimmune (autoantibodies) and immunoallergic features (rash, fever, eosinophilia) are uncommon.

Mechanism of Injury

The mechanism by which paroxetine causes liver injury is not known. Paroxetine is metabolized at least in part by the liver, mainly via the cytochrome P450 system, and hepatotoxicity may be mediated by toxic intermediates of their metabolism.

Outcome and Management

The serum aminotransferase elevations that occur on paroxetine therapy are usually self-limited and do not require dose modification or discontinuation of therapy. Acute liver failure has been reported, but is very rare with paroxetine induced liver injury as is chronic liver injury. Persons with intolerance to paroxetine 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: Citalopram, Escitalopram, Duloxetine, Fluoxetine, Fluvoxamine, Levomilnacipran, Sertraline, Venlafaxine, Vilazodone, Vortioxetine

CASE REPORT

Case 1. Serum enzyme elevations during paroxetine therapy.

[Modified from: Helmchen C, Boerner RJ, Meyendorf R, Hegerl U. Reversible hepatotoxicity of paroxetine in a patient with major depression. Pharmacopsychiatry 1996; 29: 223-6. PubMed Citation]

A 64 year old woman with long history of recurrent depression developed liver enzyme elevations 32 days after starting paroxetine. She had a seven year history of episodic depression and had received several courses of various monamine oxidase inhibitors and tricyclic antidepressants in the past. After failure of these agents for a particularly difficult episode of depression, she was started on paroxetine with regular monitoring and increase of the dosage from 5 to 60 mg per day, along with "lithium augmentation". Ten days after escalating the dose of paroxetine, she had mild nausea but improved mood. Routine laboratory testing showed elevations in serum enzymes (Table) and paroxetine was stopped. Tests for hepatitis A, B and C were negative as was ultrasonography of the abdomen. Within 14 days, serum enzymes had fallen to normal and she was switched to amitriptyline with continued improvement in depression and no enzyme elevations.

Key Points

Medication:	Paroxetine (5 to 60 mg/day)
Pattern:	Hepatocellular (R=7)
Severity:	1+ (serum enzyme elevations, mild symptoms)
Latency:	32 days
Recovery:	14 days
Other medications:	Low doses of lithium (200 mg daily)

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Alk* P (U/L)	Bilirubin (mg/dL)	Other
- 2 weeks	Pre	20	85	0.4	
Paroxetine given initially at 5 mg/day and gradually increased to 60 mg/day					
4 weeks	0	592	226	1.7	Paroxetine=203 ng/mL
	1 day	480			Lithium=0.15 mmol/L
	2 days	230	160		
	3 days	160	155		
	6 days	75	135		

Table continued from previous page.

Time After Starting	Time After Stopping	ALT* (U/L)	Alk* P (U/L)	Bilirubin (mg/dL)	Other
	10 days	45	110		
6 weeks	2 weeks	25	105	Normal	
Normal Values		**<40**	**<115**	**<1.2**	

*Estimated from Figure 1.

Comment

Convincing report of abnormal serum aminotransferase and alkaline phosphatase levels developing during somewhat high dose paroxetine therapy. The patient had few if any symptoms attributable to the liver injury and did not become jaundiced (although serum bilirubin levels rose slightly). Serum paroxetine levels were high and lithium levels were minimal. There was prompt improvement on stopping therapy. There was no cross sensitivity to tricyclic antidepressants which were subsequently used.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Paroxetine – Generic, Paxil®

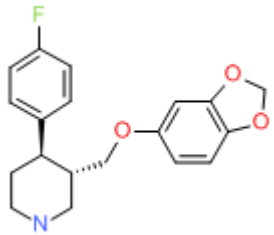
DRUG CLASS

Antidepressant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Paroxetine	61869-08-7	C19-H20-F-N-O3	

ANNOTATED BIBLIOGRAPHY

References updated: 10 January 2014

Zimmerman HJ. Antidepressants. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 493-8.

(Expert review of hepatotoxicity published in 1999; mentions one case report of acute and one of chronic drug induced liver injury due to paroxetine).

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 but paroxetine is the most frequently implicated, causing a range of clinical presentations of acute hepatitis, usually hepatocellular or mixed).

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).

Boyer WF, Blumhardt CL. The safety profile of paroxetine. J Clin Psychiatry 1992; 53: 61-66. PubMed PMID: 1531828.

(Pooled data on 4126 patients on paroxetine, 1811 comparator antidepressants and 625 placebo in clinical trials; there were "no statistically significant changes in hepatic or renal function"; one case of hepatitis possibly related to paroxetine mentioned).

Dunbar GC, Claghorn JL, Kiev A, Rickels K, Smith WT. A comparison of paroxetine and placebo in depressed patients. Acta Psychiatr Scand 1993; 87: 302-5. PubMed PMID: 8517168.

(Pooled analysis of trials of paroxetine [n=167] vs placebo [n=169] for 6 weeks; side effects more common with paroxetine, with nausea, somnolence, sweating, dry mouth and constipation; no laboratory test abnormalities noted).

Helmchen C, Boerner RJ, Meyendorf R, Hegerl U. Reversible hepatotoxicity of paroxetine in a patient with major depression. Pharmacopsychiatry 1996; 29: 223-6. PubMed PMID: 8956353.

(64 year old woman with onset of liver test abnormalities 32 days after starting paroxetine [peak bilirubin 1.7 mg/dL, ALT 592 U/L, Alk P 226 U/L, without eosinophilia], resolving within 2 weeks of stopping: Case 1).

Benbow SJ, Gill G. Paroxetine and hepatotoxicity. Br Med J 1997; 314: 1387. PubMed PMID: 9161313.

(54 year old woman found to have elevated AST [256 U/L] with normal bilirubin and Alk P 10 months after starting paroxetine; 6 months later AST was still elevated [299 U/L] and liver biopsy showed chronic hepatitis; AST fell with stopping paroxetine).

de Man RA. [Severe hepatitis attributed to paroxetine (Seroxat)]. Ned Tijdschr Geneeskund 1997; 141: 540-2. PubMed PMID: 9190513.

(52 year old man with chronic hepatitis B and cirrhosis developed severe flare of hepatitis 10 months after starting paroxetine [bilirubin ~2.6 mg/dL, AST rising to 800 U/L] and appearance of ascites, improving with stopping paroxetine, no information on change of HBV DNA levels).

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).

Grohmann R, Rüther E, Engel RR, Hippius H. Assessment of adverse drug reactions in psychiatric inpatients with the AMSP drug safety program: methods and first results for tricyclic antidepressants and SSRI. Pharmacopsychiatry 1999; 32: 21-8. PubMed PMID: 10071179.

(Analysis of reporting of adverse events among inpatients in 29 German hospitals between 1993 to 1997; 896 severe adverse events among 48,564 patients [1.8%], both total and hepatic events were more common with tricyclics than SSRIs).

Cadranel JF, DiMartino V, Cazier A, Pras V, Bachmeyer C, Olympio P, Gonzenbach A, et al. Atrium and paroxetine-related severe hepatitis. J Clin Gastroenterol 1999; 28: 52-5. PubMed PMID: 9916669.

(Two cases; 31 and 35 year old women developed hepatitis 4 and 15 months after starting "Atrium" and paroxetine [bilirubin 11.6 and 5.8 mg/dL, ALT 2010 and 539 U/L, Alk P 86 and 243 U/L], resolving within 3 and 6 months of stopping both drugs; paroxetine may have predisposed to Atrium hepatotoxicity).

Odeh M, Misselevech I, Boss JH, Oliven A. Severe hepatotoxicity with jaundice associated with paroxetine. Am J Gastroenterol 2001; 96: 2494-6. PubMed PMID: 11513198.

(49 year old man with ulcerative colitis on 5-aminosalicyclic acid [a-ASA] developed jaundice and pruritus 6 weeks after starting paroxetine [bilirubin 10.1 mg/dL, ALT 561 U/L, Alk P 455 U/L], resolving within 10 weeks of stopping despite restarting 5-ASA).

Azaz-Livshits T, Hershko A, Ben-Chetrit E. Paroxetine associated hepatotoxicity: a report of 3 cases and a review of the literature. Pharmacopsychiatry 2002; 35: 112-5. PubMed PMID: 2107856.

(3 cases of paroxetine hepatotoxicity; case 1 was a 49 year old man who developed rash and fever 18 days after starting paroxetine and trazodone [bilirubin 1.3 rising to 8.6 mg/dL, ALT 975 U/L, Alk P normal], resolving within 4 weeks of stopping; cases 2 and 3 were 80 and 85 year old men who developed abnormal liver tests 2-3 weeks after starting paroxetine [bilirubin normal, ALT 416 and 630 U/L], resolving rapidly upon stopping, but both patients had multiple medical conditions, heart disease, renal failure and sepsis).

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 similar in rate ~1-3 per 100,000 patient-years of exposure, except for nefazodone=29/100,000).

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).

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).

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 antidepressants; 30 year old woman developed jaundice 8 weeks after starting citalopram [bilirubin 4.4 mg/dL, AST 33 U/L, Alk P 637 U/L], resolving within 2 months of stopping; 63 year

old man developed jaundice 3 months after starting the tricylcic dothiepin [bilirubin 9.4 mg/dL, AST 40 U/L, Alk P 600 U/L], resolving within 3 months of stopping with corticosteroid therapy and later tolerating fluoxetine for 12 months, but redeveloping a similar pattern 2 months after starting paroxetine [bilirubin 15.2 mg/dL, AST 36 U/L, Alk P 544 U/L], resolving within 6 months of stopping).

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: 5052513.

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

Colakoglu O, Tankurt E, Unsal B, Ugur F, Kupelioglu A, Buyrac Z, Akpinar Z. Toxic hepatitis associated with paroxetine. Int J Clin Pract 2005; 59: 861-2. PubMed PMID: 15963219.

(62 year old man with renal failure and anti-HCV developed jaundice 3 months after starting paroxetine [bilirubin 47.1 mg/dL, ALT 1321 U/L, Alk P 1321 U/L, eosinophils 6%, protime 18.2 sec, HCV RNA negative], resolving 3 months after stopping).

Guzmán Ruiz O, Ramírez Martín del Campo M, Fernandez López I, Romero Gómez M. [Hepatotoxicity induced by paroxetine]. Med Clin (Barc) 2005; 124: 399. Spanish. PubMed PMID: 15766517.

(32 year old woman with type 1 diabetes developed ketoacidosis and mild enzyme elevations 4 months after starting paroxetine [normal bilirubin and Alk P, ALT 220 U/L], which resolved rapidly upon stopping, and she later tolerated citalopram without recurrence).

Pinzani V, Peyriere H, Hillaire-Buys D, Pageaux GP, Blayac BP, Larrey D. Specific serotonin recapture inhibitor (SSRI) antidepressants: hepatoxicity assessment in a large cohort in France. J Hepatol 2006; 44: S256. Not in PubMed

(Abstract: analysis of French Pharmacovigilance data on SSRIs found 63 cases of hepatotoxicity from paroxetine, 45 fluoxetine, 30 citalopram, 18 sertraline, and 2 fluvoxamine).

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 1993-2000, 3 were attributed to paroxetine and 3 to fluoxetine with a relative risk of injury to rate of use in the population of 3.0 and 1.8, respectively).

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

(Review of drug induced liver injury and reports of injury from MAO inhibitors, SSRIs, tricyclics and atypical agents).

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 were attributed to duloxetine, 3 to atomoxetine, 2 to fluoxetine, 2 to bupropion, and 1 to sertraline as single agents; no cases were attributed to paroxetine).

Marks DM, Park M-H, Ham B-J, Han C, Patkar AA, Masand PS, Pae C-U. Paroxetine: safety and tolerability issues. Expert Opin Drug Saf 2008; 7: 783-94. PubMed PMID: 18983224.

(Review of pharmacology and safety of paroxetine; side effects are similar to those of other SSRIs, discontinuation rates of 9-20%; weight gain averages 3.6% and sexual dysfunction ranges from 22-65%, both of which are higher than with other SSRIs; no discussion of hepatotoxicity).

Pompili M, Tittoto P, Mascianà R, Gasbarrini G, Rapaccini GL. Acute hepatitis associated with use of paroxetine. Intern Emerg Med 2008; 3: 275-7. PubMed PMID: 18265937.

(84 year old woman with atrial fibrillation and cerebrovascular disease presented with confusion and had rises in ALT [13→2110 U/L], Alk P [180→277 U/L], and bilirubin [1.0→2.5 mg/dL], and abnormal INR [2.1] and ammonia [335 µmol/L] within a week of starting paroxetine, resolving within 15 days of stopping).

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, one attributed to venlafaxine and one to fluoxetine, but none to paroxetine).

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 paroxetine and other antidepressants were not listed).

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

(Review of antidepressant induced liver injury).

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, none of which were attributed to paroxetine).