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Pregabalin

Updated: January 22, 2014.

OVERVIEW

Introduction

Pregabalin is an inhibitor of neuronal activity used for therapy of neuropathy and as an anticonvulsant. Therapy with pregabalin is not associated with serum aminotransferase elevations, and clinically apparent liver injury from pregabalin has been reported but appears to be quite rare.

Background

Pregabalin (pre gab' a lin) is a structural analogue of gamma-aminobutyric acid (GABA) but is novel in its activity, having no effects on GABA-A or GABA-B receptors. Instead, the neuronal acitivity of pregabalin appears to be mediated by its binding to the alpha-2-delta subunit of the presynaptic voltage-gated calcium channel whcih leads to a decrease in release of neuroexcitatory neurotransmitters by hyperexcited neurons. Pregabalin has been shown to be effective in reducing neuropathic pain from diabetic and postherpetic neuropathy and is an effective anticonvulsant. Pregabalin was approved for use in the United States in 2004. Current indications include diabetic and post-herpetic neuropathy and as adjunctive therapy of partial onset seizures. Pregabalin is also used for fibromyalgia and off-label for generalized anxiety disorders and migraine. Pregabalin is available in capsules in varying concentrations from 25 to 300 mg under the brand name of Lyrica. The recommended initial dose for neuropathic pain is 50 to 75 mg two to three times daily, the maximum dose being 300 mg daily. Higher doses are used in treating seizures. The dose should be increased and tapered gradually. The most common side effects of pregabalin are dose related and include peripheral edema, weight gain, dizziness, somnolence, confusion, headache, blurred vision, tremor and ataxia.

Hepatotoxicity

Limited data is available on the hepatotoxicity of pregabalin. In prelicensure clinical trials in diabetic neuropathy and epilepsy, therapy with pregabalin was not associated with an increased frequency of serum aminotransferase elevations or liver toxicity. Since its approval and more wide scale use, however, pregabalin has been linked to rare instances of clinically apparent liver injury. Most cases were mild and frequently without jaundice. The latency to onset of injury was short, symptoms of liver injury arising within 3 to 14 days. Both cholestatic and hepatocellular patterns of injury have been reported. Signs of hypersensitivity (fever, rash, eosinophilia) and autoimmunity were not present. Some cases have been severe and associated with marked jaundice and prolongation of the prothrombin time, but all cases ultimately resolved after the medication was stopped without evidence of residual injury.

Mechanism of Injury

The low rate of significant hepatotoxicity from pregabalin may be due to its minimal hepatic metabolism and rapid urinary excretion. The injury is clearly idiosyncratic and either immunologic or metabolic causes are possible.

Outcome and Management

The case reports of hepatic injury due to pregabalin were followed by complete recovery without evidence of residual or chronic injury. There is no information about cross reactivity with other compounds having similar structure (gabapentin).

Drug Class: Anticonvulsants

CASE REPORT

Case 1. Mild cholestatic hepatitis attributed to pregabalin therapy.

[Modified from: Crespo Pérez L, Moreira Vicente V, Manzano Fernández R, García Aguilera XA. [Cholestasis associated with pregabalin treatment] Med Clin (Barc) 2008; 130: 157-8. Spanish. PubMed Citation]

A 61 year old man underwent laminectomy for spinal stenosis and was started on pregabalin 2 weeks later. Within 2 days he developed dizziness, blurred vision, somnolence and fatigue, which worsened when the dose was increased from 75 to 150 mg/day one week later. Because of persistence of symptoms, blood tests were taken 11 days after starting therapy which revealed moderate enzyme elevations (Table). The patient had a history of hypertension and gout for which he took amlodipine (5 mg/day), candesartan (16 mg/day) and allopurinol (100 mg/day) chronically. Before the laminectomy, serum enzymes were tested and were normal. After surgery, he received metamizole (an NSAID not available in the US) for five days. Physical examination showed no jaundice, rash or signs of chronic liver disease. Tests for hepatitis A, B, C, D, and E, for HIV and for autoantibodies were negative. Abdominal ultrasound and MRCP were normal. Pregabalin was stopped and all symptoms except for mild fatigue, resolved rapidly. Reintroduction of pregabalin a few days later led to an immediate return of symptoms, but blood tests were not taken during the rechallenge. The abnormal enzyme values rapidly improved once pregabalin was stopped and were normal two months later.

Key Points

Medication:	Pregabalin (75→150 mg daily)
Pattern:	Mixed (R=2.1)
Severity:	1+ (enzyme elevations without jaundice)
Latency:	2 days to onset of symptoms, 11 days to laboratory abnormalities
Recovery:	Rapid (2 to 8 weeks)
Other medications:	Amlodipine, candesartan, and allopurinol chronically. Metamizole for 5 day 3 weeks before onset.

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre		Normal	Normal	Normal	Preoperative evaluation
0	Pregabalin started: 75 mg/day increasing to 150 mg/day one week later				
11 days	0	307	476	1.7	GGT 1546 U/L

Table continued from previous page.

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
22 days	10 days	37	174	1.0	GGT 542 U/L
11 weeks	10 weeks	32	125	0.9	GGT 44 U/L
Normal Values		**<40**	**<130**	**<1.2**	

Comment

Other causes of acute liver disease were excluded. The rechallenge was somewhat convincing, but the role of pregabalin in causing liver injury was not completely proven because of the lack of testing immediately before and after the two day rechallenge (on days 13-14 after starting). Based on the "R" value, the pattern of enzyme elevations was "mixed," but the subsequent values and GGT elevations suggest that the injury was cholestatic. Most published cases of liver injury attributed to pregabalin have been marked by a short latency (3 to 14 days) and a rapidly resolving, self-limiting course.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Pregabalin – Lyrica®

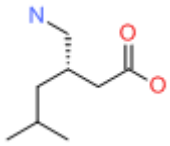
DRUG CLASS

Anticonvulsants

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Pregabalin	148553-50-8	C8-H17-N-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 22 January 2014

Zimmerman HJ. Anticonvulsants. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 498-516.

(Expert review of liver injury due to anticonvulsants published in 1999, before the clinical availability of pregabalin which is not discussed).

Pirmohamed M, Leeder SJ. Anticonvulsant agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013: pp 423-41.

(Review of anticonvulsant induced liver injury does not specifically discuss pregabalin).

McNamara JO. Pharmacology of the epilepsies. In, Brunton LL, Chabner BA, Knollman BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 583-608.

(Textbook of pharmacology and therapeutics).

Huckle R. Pregabalin (Pfizer). Curr Opin Investig Drugs 2004; 5: 82-9. PubMed PMID: 14983979.

(History of development of pregabalin and summary of information on mechanisms of action, pharmacology, pharmacokinetics, and clinical data supporting indications; no information on liver adverse events).

Ben-Menachem E. Pregabalin pharmacology and its relevance to clinical practice. Epilepsia 2004; 45 (Suppl 6): 13-8. PubMed PMID: 15315511.

(Summary of pharmacology and pharmacokinetics of pregabablin; it has no hepatic metabolism and does not induce P450 enzymes).

Kavoussi R. Pregabalin: From molecule to medicine. Eur Neuropsychopharmacol 2006; 16 (Suppl 2): S128-33. PubMed PMID: 16765030.

(Summary of mechanism of action and clinical experience with pregabalin in generalized anxiety disorder; no mention of hepatic adverse events).

Tassone DM, Boyce E, Guyer J, Nuzum D. Pregabalin: a novel gamma-aminobutyric acid analogue in the treatment of neuropathic pain, partial-onset seizures, and anxiety disorders. Clin Ther 2007; 29: 26-48. PubMed PMID: 17379045.

(Review of efficacy and safety of pregabalin; major side effects were CNS related including dizziness, somnolence, headache, and ataxia, also edema and weight gain; withdrawal symptoms included anxiety, irritability and nervousness: "…there were no significant differences in changes in blood chemistry or hematology tests…").

Crespo Pérez L, Moreira Vicente V, Manzano Fernández R, García Aguilera XA. [Cholestasis associated with pregabalin treatment] Med Clin (Barc) 2008; 130: 157-8. Spanish. PubMed PMID: 18279637.

(61 year old man with neuropathic pain after laminectomy developed symptoms of dizziness and fatigue within 2 days, and liver test abnormalities at 11 days after starting pregabalin [bilirubin 1.2 mg/dL, ALT 307 U/L, Alk P 476 U/L], symptoms recurring with rechallenge, and all signs of injury resolving within 2 months of stopping: Case 1).

Einarsdottir S, Björnsson E. Pregabalin as a probable cause of acute liver injury. Eur J Gastroenterol Hepatol 2008; 20: 1049. PubMed PMID: 18787478.

(61 year old man developed nausea followed by jaundice 8 days after starting pregabalin [bilirubin 10.7 mg/dL, ALT 35 times ULN, INR 3.8], resolving completely within 24 weeks).

Freeman R, Durso-Decruz E, Emir B. Efficacy, safety, and tolerability of pregabalin treatment for painful diabetic peripheral neuropathy: findings from seven randomized, controlled trials across a range of doses. Diabetes Care 2008; 31: 1448-54. PubMed PMID: 18356405.

(Pooled data from 7 trials of pregabalin given for 5-13 weeks vs placebo in 1510 patients; common side effects were edema, weight gain, dizziness and somnolence with "…no clinically meaningful changes in laboratory values from baseline.").

Stein DJ, Baldwin DS, Baldinetti F, Mandel F. Efficacy of pregabalin in depressive symptoms associated with generalized anxiety disorder: a pooled analysis of 6 studies. Eur Neuropsychopharmacol 2008; 18: 422-30. PubMed PMID: 18359203.

(Pooled analysis in >1000 patients with generalized anxiety disorder showed improvement with higher doses, but provided no information on tolerance or side effects).

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, none were linked to pregabalin).

[Hepatic adverse effects of pregabalin (Lyrica)]. Lakartidningen 2010; 107 (4): 194. Swedish. PubMed PMID: 20333975.

Johannessen Landmark C, Patsalos PN. Drug interactions involving the new second- and third-generation antiepileptic drugs. Expert Rev Neurother 2010; 10: 119-40. PubMed PMID: 20021326.

(Review of drug-drug interactions; pregabalin has not been implicated in clinical signficant drug interactions with other major anticonvulsants).

Doğan S, Ozberk S, Yurci A. Pregabalin-induced hepatotoxicity. Eur J Gastroenterol Hepatol 2011; 23: 628. PubMed PMID: 21654262.

(28 year old woman developed jaundice 4 months after starting pregabalin [bilirubin 16.3 mg/dL, ALT 26 times ULN, INR 1.91], resolving within 2 months of stopping).

Sendra JM, Junyent TT, Pellicer MJ. Pregabalin-induced hepatotoxicity. Ann Pharmacother 2011; 45: e32. Epub 2011 Jun 7. PubMed PMID: 21652790.

(59 year old man developed serum enzyme elevations 14 days after starting pregabalin [bilirubin 1.3 mg/dL, ALT 1582 U/L, Alk P 488 U/L], resolving in 4 months; patient had preexisting abnormalities and also received levofloxacin).

Zaccara G, Gangemi P, Perucca P, Specchio L. The adverse event profile of pregabalin: a systematic review and meta-analysis of randomized controlled trials. Epilepsia 2011; 52: 826-36. PubMed PMID: 21320112.

(Analysis of 38 double-blind trials of pregabalin identified 20 adverse events that were more common with pregabalin than comparator arms and were mostly dizziness, vertigo, ataxia, diplopia, tremor, somnolence and confusion; even in non-frequently mentioned side effects, ALT elevations and hepatotoxicity were not listed).

Toth C. Drug safety evaluation of pregabalin. Expert Opin Drug Saf 2012; 11: 487-502. PubMed PMID: 22468635.

(Review of structure, mechanism of action, pharmacokinetics, clinical uses and safety of pregabalin; common side effects include dizziness, sedation, dry mouth, weight gain and edema, rash and hypersensitivity reactions are rare; no mention of hepatotoxicity or ALT changes during therapy).

Drugs for epilepsy. Treat Guidel Med Lett 2013; 11: 9-18. PubMed PMID: 23348233.

(Concise review of the drugs of choice for epilepsy; pregabalin is listed as an alternate drug of choice for partial onset seizures; side effects include somnolence, dizziness, ataxia, confusion, weight gain, dry mouth, blurred vision and edema; ALT elevations and liver injury are not mentioned).

Bamanikar A, Dhobale S, Lokwani S. Pregabalin hypersensitivity in a patient treated for postherpetic neuralgia. Indian J Pharmacol 2013; 45: 522-3. PubMed PMID: 24130391.

(40 year old man developed fever, rash and facial swelling 2 weeks after starting pregabalin for post-herpetic neuralgia [bilirubin normal, ALT 250 U/L, Alk P normal], resolving on oral prednisolone and within a few months of stopping pregabablin).