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Gabapentin

Updated: February 25, 2018.

OVERVIEW

Introduction

Gabapentin is a unique anticonvulsant that is used as adjunctive therapy in management of epilepsy and for neuropathic pain syndromes. Therapy with gabapentin is not associated with serum aminotransferase elevations, but several cases of clinically apparent liver injury from gabapentin have been reported.

Background

Gabapentin (gab" a pen' tin) is a structural analogue of gamma-aminobutryic acid (GABA), but demonstrates little or no interaction with GABA receptors and does not appear to alter GABA uptake, synthesis or metabolism. While initially believed to act on the GABA-ergic neurotransmitter system, the actual mechanism of action of gabapentin as an anticonvulsant and agent for neuropathy is unknown. Gabapentin was approved for use in the United States in 1993 and is a widely used medication with more than 18 million prescriptions filled yearly. Current indications include add-on therapy for partial seizures which do not have adequate control with other anticonvulsants, and to reduce neuropathic pain from diabetic and postherpetic neuropathy. Gabapentin is available as capsules or tablets of 100, 300, 400, 600 and 800 mg and in oral solution for pediatric use generically and under the brand names Neurontin and Gabarone. The recommended initial dose for adults is 300 mg three times daily increasing as needed to a maximum dose of 1800 mg daily. The most common side effects of gabapentin are dose related and include dizziness, somnolence, tremor, ataxia, blurred vision, anxiety, and gastrointestinal upset or nausea. Rare, but potentially severe adverse events include hypersensitivity reactions such as angioneurotic edema, drug rash with eosinophilia with systemic manifestations (DRESS syndrome) and Stevens Johnson syndrome.

Hepatotoxicity

Limited data are available on the hepatotoxicity of gabapentin. In clinical trials in diabetic neuropathy and epilepsy, therapy with gabapentin was not associated with an increased frequency of serum aminotransferase elevations or liver toxicity. Rare individual case reports of liver injury from gabapentin have been published, although the causal relationship of gabapentin with the liver injury was not always clear. The latency to onset in these reports was 1 to 8 weeks and associated with cholestatic pattern of enzyme elevations. Fever and rash have been described but not autoantibody formation. Reported cases have been mild to moderate in severity and self-limited in course. In view of the wide-scale use of gabapentin, liver injury with symptoms or jaundice is clearly quite rare.

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

Mechanism of Injury

The apparent absence or low rate of significant hepatotoxicity from gabapentin may be due to its minimal hepatic metabolism and rapid urinary excretion.

Outcome and Management

The case reports of hepatic injury due to gabapentin were followed by complete recovery without evidence of residual or chronic injury. No cases of acute liver failure or chronic liver injury due to gabapentin have been described. There is no information about cross reactivity with other compounds having similar structure (pregabalin). In general, gabapentin is well tolerated in patients with hypersensitivity reactions to other anticonvulsants.

Drug Class: Anticonvulsants

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Gabapentin – Neurontin®

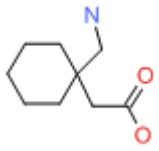
DRUG CLASS

Anticonvulsants

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Gabapentin	60142-96-3	C9-H17-N-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 25 February 2018

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 anticonvulsants and liver injury published in 1999; gabapentin 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 423-42.

(Review of anticonvulsant induced liver injury; gabapentin is not discussed).

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. 583-607.

(Textbook of pharmacology and therapeutics)

Chadwick D. Gabapentin. Lancet 1994; 343: 89-91. PubMed PMID: 7903783.

(Review of the clinical uses of gabapentin largely as add-on to other anticonvulsants. Most common side effects were somnolence, dizziness, ataxia, fatigue, nystagmus, headache, tremor, diplopia, nausea and rhinitis. "No serious idiosyncratic reactions have been identified with gabapentin and, in particular, there is no evidence of hypersensitivity reactions…").

US Gabapentin Study Group. The long-term safety and efficacy of gabapentin (Neurotin) as add-on therapy in drug-resistant partial epilepsy. Epilepsy Res 1994; 18: 67-73. PubMed PMID: 8088258.

(Systematic review; ALT elevations occur in 4% of children on phenytoin, 6% on valproate, 1% on carbamazepine, but none reported on tiagabine or gabapentin).

Hamer HM, Morris HH. Hypersensitivity syndrome to antiepileptic drugs: a review including new anticonvulsants. Cleve Clin J Med 1999; 66: 239-45. PubMed PMID: 10199060.

(Clinical review of anticonvulsant hypersensitivity syndrome, which occurs in 1 to 5 per 10,000 users of aromatic anticonvulsants with higher risk in African Americans and affected siblings; liver involvement common, but most cases are anicteric; other manifestations include facial edema, lymphadenopathy, bone marrow aplasia, pseudolymphoma, thyroiditis, interstitial nephritis; not linked to gabapentin).

Hamer HM, Morris HH. Successful treatment with gabapentin in the presence of hypersensitivity syndrome to phenytoin and carbamazepine: a report of three cases. Seizure 1999; 8: 190-2. PubMed PMID: 10356381.

(3 patients developed rash, fever, lymphadenopathy and eosinophilia 4-6 weeks after starting either phenytoin or carbamazepine [bilirubin 0.5-1.8 mg/dL, ALT 866-1402 U/L, Alk P 69-364 U/L], resolving after stopping and not recurring during gabapentin therapy).

Wong ICK, Lhatto SD. Adverse reactions to new anticonvulsant drugs. Drug Safety 2000; 23: 35-56. PubMed PMID: 10915031.

(Review of side effects of new anticonvulsants: side effects of gabapentin are largely CNS related and include somnolence, dizziness, diplopia, ataxia, tremor and nausea, but no mention of liver toxicity and overdose was associated with lethargy only).

Ragucci MV, Cohen JM. Gabapentin-induced hypersensitivity syndrome. Clin Neuropharmacol 2001; 24: 103-5. PubMed PMID: 11307046.

(72 year old man developed confusion and fever 8 days after starting gabapentin; was then given levofloxacin and developed rash liver abnormalities 2 days later [bilirubin normal, GGT 296 U/L, Alk P 218 U/L], resolving 15 days after stopping gabapentin; case did not fulfill criteria for hypersensitivity syndrome and was complicated by use of levofloxacin).

Lasso-de-la-Vega MC, Zapater P, Such J, Pérez-Mateo M, Horga JF. Gabapentin-associated hepatotoxicity. Am J Gastroenterol 2001; 96: 3460-2. PubMed PMID: 11774985.

(60 year old man developed skin rash and eosinophilia 1 month after starting gabapentin and 1 day after starting ciprofloxacin; 1 week later was found to be jaundiced [bilirubin not given, ALT ~320 U/L, GGT ~1000 U/L], gabapentin was decreased in dose and stopped a week later and laboratory tests improved concurrently: ciprofloxacin might also have been responsible).

Hauben M. Re: Lasso-de-la-Vega et al. Gabapentin as a probable cause of hepatotoxicity and eosinophilia. Am J Gastroenterol 2002; 97: 2156-7. PubMed PMID: 12190207.

(Letter from industry sponsor suggesting that hypersensitivity reaction in patient described by Lasso-de-la-Vega [2001] was more likely due to ciprofloxacin than gabapentin).

Bureau C, Poirson H, Péron JM, Vinel JP. [Gabapentine-induced acute hepatitis] Gastroenterol Clin Biol 2003; 27: 1169-70. French. PubMed PMID: 14770125.

(Patient developed jaundice, fever and pain 2 months after starting gabapentin, had inflamed gallbladder and underwent cholecystectomy, but bilirubin continued to rise [bilirubin either 2.7 or 27 mg/dL, ALT 8 times ULN, Alk P 12 times ULN]; gabapentin was stopped, ultimate complete recovery in ~1 month; unclear whether gabapentin or gallstones were the cause).

Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, Mason A, et al. Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. Health Technol Assess 2005; 9: 1-157, iii-iv. PubMed PMID: 15842952.

(Extensive systematic review of anticonvulsant medications including assessment of serious, rare and long term adverse events; severe side effects are rare with gabapentin; no mention of hepatotoxicity).

LaRoche SM. A new look at the second-generation antiepileptic drugs: a decade of experience. Neurologist 2007; 13: 133-9. PubMed PMID: 17495757.

(Review of second generation anticonvulsants approved since 1994 including felbamate, gabapentin, lamotrigine, topiramate, tiagabine, levetiracetam, oxcarbazepine, zonisamide and pregabalin; serious side effects are rare and no mention of liver toxicity from gabapentin).

Himmerich H, Nickel T, Dalal MA, Müller MB. [Gabapentin treatment in a female patient with panic disorder and adverse effects under carbamazepine during benzodiazepine withdrawal] Psychiatr Prax 2007; 34: 93-4. German. PubMed PMID: 17124639.

(70 year old woman with panic disorder and benzodiazepine dependence who developed liver test abnormalities on carbamazepine [ALT 103 U/L, GGT 309 U/L] tolerated long term therapy with gabapentin, which allowed withdrawal of benzodiazepines without recurrence of ALT elevations).

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 between 2004 and 2008, valproate accounted for 6, lamotrigine 5, phenytoin 5, gabapentin and topiramate 1 each but details not provided).

Björnsson E. Hepatotoxicity associated with antiepileptic drugs. Acta Neurol Scan 2008; 118: 281-90. PubMed PMID: 18341684.

(Review of all anticonvulsant induced liver injury; neither gabapentin or pregabalin are discussed).

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

(Concise review of drugs of choice for epilepsy; gabapentin is FDA approved as adjunctive therapy of partial seizures and adverse effects include somnolence, dizziness, ataxia, fatigue, and blurred vision; no mention of hepatotoxicity or ALT elevations).

Fuzier R, Serres I, Guitton E, Lapeyre-Mestre M, Montastruc JL; French Network of Pharmacovigilance Centres. Adverse drug reactions to gabapentin and pregabalin: a review of the French pharmacovigilance database. Drug Saf 2013; 36: 55-62. PubMed PMID: 23315296.

(Among 725 spontaneous adverse event reports related to gabapentin made to the French Pharmacovigilance System between 1995 and 2009, liver ranked second to neuropsychiatric reactions in frequency [n=90, 12%], 37 of which were "hepatitis", half of which were serious, 8 were "probable" or "likely" and one fatal, but no specific details given).

Gabapentin and pregabalin: hepatic and haematological toxicity. Prescrire Int 2014; 23 (154): 267. PubMed PMID: 25954794.

(Review of spontaneous reports of adverse events attributed to gabapentin from a French registry [Fuzier 2013] identified 90 cases of liver damage, gabapentin being the only suspect drug in 10 cases of "hepatitis", one of which was fatal).

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, 40 cases [4.5%] were attributed to anticonvulsants, including 3 to gabapentin, the latency to onset being 3-6 weeks, with a mixed or cholestatic pattern of injury and a moderate, self-limited course).

Zaccara G, Giovannelli F, Giorgi FS, Franco V, Gasparini S, Benedetto U. Tolerability of new antiepileptic drugs: a network meta-analysis. Eur J Clin Pharmacol 2017; 73: 811-7. PubMed PMID: 28378057.

(Metanalysis of the comparative tolerability of 18 new anticonvulsant agents including gabapentin, found lowest rates of withdrawal for adverse events with levertiracetam, brivaracetam, and gabapentin with highest rates with eslicarbazepine, oxcarbazepine, lacosamide and topiramate).

Drugs for epilepsy. Med Lett Drugs Ther 2017; 59 (1526): 121-30. PubMed PMID: 28746301.

(Concise review of the drugs available for therapy of epilepsy lists gabapentin as a second line, alternative therapy of partial onset seizures and mentions common side effects of somnolence, dizziness, ataxia, fatigue, blurred vision and confusion, but does not mention ALT elevations or hepatotoxicity).

Vidaurre J, Gedela S, Yarosz S. Antiepileptic drugs and liver disease. Pediatr Neurol 2017; 77: 23-36. PubMed Citation

(Summary of the hepatotoxicity of major anticonvulsant medications including gabapentin which has no hepatic metabolism, so specific recommendation for dose modification because of liver disease, a minimal potential for drug interations and low assocation with hepatotoxicity).