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Baclofen

Updated: January 30, 2017.

OVERVIEW

Introduction

Baclofen is a centrally acting muscle relaxant commonly prescribed for spasticity in patients with multiple sclerosis. Baclofen has not been linked to rare instances of mild, self-limited, clinically apparent liver injury.

Background

Baclofen (bak' loe fen) is a gamma-amino butyric acid (GABA) derivative that acts as an agonist of the GABA B receptor, thereby activating potassium channels and reducing calcium conductance leading to hypotonia and muscle relaxation. Baclofen acts primarily at the level of the spinal cord, inhibiting synaptic reflexes. Baclofen reduces the number and severity of muscle spasms and relieves pain, clonus and muscle rigidity due to spasticity. Baclofen is indicated primarily for treatment of spasticity from spinal cord injuries and multiple sclerosis. It has been used off label as adjunctive therapy to help with alcohol abstinence and withdrawal. Baclofen was approved for use in the United States in 1977 and is widely used with several million prescriptions filled yearly. Baclofen is available in various generic forms as well as under the brand names of Lioresal and Remular in tablets of 10 or 20 mg and in formulations for intrathecal injections of 0.5 mg/mL. The recommended adult dose for spasticity is 10 to 20 mg orally three to four times daily. The dose should be increased and tapered gradually. The most common side effects of baclofen are nausea, drowsiness, confusion, dizziness and fatigue.

Hepatotoxicity

Limited data are available on the potential hepatotoxicity of baclofen. Among the many clinical trials evaluating the safety and efficacy of baclofen, none mentioned hepatic toxicity or rates of serum ALT elevations occurring during chronic therapy. The product insert starts that 5% of treated patients develop mild serum aminotransferase elevations, but little documentation is available on the significance, severity or duration of these abnormalities. A single case of mild and self-limited hepatitis attirbuted to baclofen has been published. The latency to onset was 3 months, the pattern of injury was hepatocellular, and recovery was rapid and complete, all laboratory tests being normal within a few weeks of stopping.

Likelihood score: D (Possible, rare cause of clinically apparent liver injury).

Mechanism of Injury

The apparent absence of significant hepatotoxicity from baclofen may be due to its minimal hepatic metabolism (~15%) and rapid urinary excretion.

Outcome and Management

The minor ALT elevations associated with chronic baclofen use are usually asymptomatic and transient. Any elevation of greater than 10 times the upper limit of normal or persistence of abnormalities greater than 5 times the upper limit of normal should lead to discontinuation. Cases of clinically apparent liver injury have been self-limited in course and outcome and there have been no reports of acute liver failure, chronic hepatitis or vanishing bile duct syndrome associated with its use. There is no reason to suspect cross sensitivity to liver injury among the various muscle relaxants.

Drug Class: Muscle Relaxants

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Baclofen – Generic, Lioresal®

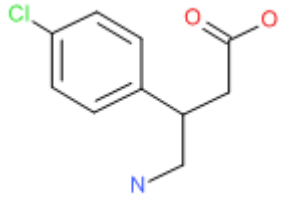
DRUG CLASS

Autonomic Agents: Muscle Relaxants, Central

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Baclofen	1134-47-0	C10-H12-Cl-N-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 30 January 2017

Zimmerman HJ. Muscle spasmolytics. In, Hepatotoxicity: The Adverse Effects of Drugs and Other Chemicals on the Liver. 2nd Ed. Philadelphia: Lippincott, 1999. p. 544-45.

(Expert review of hepatotoxicity published in 1999; mentions baclofen has been used for decades, but specific reports of hepatic injury are scanty).

Hudgson P, Weightman D, Cartlidge NE. Clinical trial of baclofen against placebo. Postgrad Med J 1972; 48 (Suppl 5): 37-40. PubMed PMID: 4585729.

(23 patients treated with baclofen in a placebo controlled trial; central nervous system side effects discussed, but no mention of hepatotoxicity).

Brogden RN, Speight TM, Avery GS. Baclofen: a preliminary report of its pharmacological properties and therapeutic efficacy in spasticity. Drugs 1974; 8: 1-14. PubMed PMID: 4154834.

(Review of preliminary studies of baclofen including side effects; does not mention ALT abnormalities or hepatotoxicity).

Cartlidge NE, Hudgson P, Weightman D. A comparison of baclofen and diazepam in the treatment of spasticity. J Neurol Sci 1974; 23: 17-24. PubMed PMID: 4850175.

(Controlled trial in 49 patients discusses central nervous system side effects, but does not mention ALT abnormalities or hepatotoxicity).

Basmajian JV. Lioresal(baclofen) treatment of spasticity in multiple sclerosis. Am J Phys Med 1975; 54: 175-7. PubMed PMID: 1098477.

(Double-blind cross over trial of placebo vs baclofen for 4 weeks; no mention of hepatotoxicity).

From A, Heltberg A. A double-blind trial with baclofen (Lioresal) and diazepam in spasticity due to multiple sclerosis. Acta Neurol Scand 1975; 51: 158-66. PubMed PMID: 1090103.

(Double-blind cross over trial in 17 patients; major side effect was sedation; no mention of ALT elevations or hepatotoxicity).

Duncan GW, Shahani BT, Young RR. An evaluation of baclofen treatment for certain symptoms in patients with spinal cord lesions. A double-blind, cross-over study. Neurology 1976; 26: 441-6. PubMed PMID: 772461.

(Double-blind cross over study in 22 patients; no mention of ALT monitoring or hepatotoxicity).

Milla PJ, Jackson AD. A controlled trial of baclofen in children with cerebral palsy. J Int Med Res 1977; 5: 398-404. PubMed PMID: 338390.

(Cross over study of baclofen vs placebo in 20 children; no mention of ALT monitoring or hepatotoxicity).

Sachais BA, Logue JN, Carey MS. Baclofen, a new antispastic drug. A controlled, multicenter trial in patients with multiple sclerosis. Arch Neurol 1977; 34: 422-8. PubMed PMID: 327987.

(106 patients given baclofen or placebo for 5 weeks; no laboratory abnormalities found and no mention of hepatotoxicity).

Feldman RG, Kelly-Hayes M, Conomy JP, Foley JM. Baclofen for spasticity in multiple sclerosis. Double-blind cross-over and three-year study. Neurology 1978; 28: 1094-8. PubMed PMID: 362234.

(23 patients in a 10 week cross over trial and then given baclofen for 3 years; laboratory tests taken every 3 months showed no abnormality and results make no mention of hepatotoxicity).

Ghose K, Holmes KM, Matthewson K. Complications of baclofen overdosage. Postgrad Med J 1980; 56: 865-7. PubMed PMID: 7267501.

(Overdose of baclofen led to coma and respiratory failure, but no mention of hepatotoxicity).

Lipscomb DJ, Meredith TJ. Baclofen overdose. Postgrad Med J 1980; 56: 108-9. PubMed PMID: 6771749.

(Overdose of baclofen led to coma and respiratory failure, but no mention of hepatotoxicity).

Smolenski C, Muff S, Smolenski-Kautz S. A double-blind comparative trial of new muscle relaxant, tizanidine (DS 103-282), and baclofen in the treatment of chronic spasticity in multiple sclerosis. Curr Med Res Opin 1981; 7: 374-83. PubMed PMID: 7016449.

(21 patients were treated with tizanidine or baclofen for 6 weeks; authors make no mention of hepatotoxicity of either drug).

Chui LK, Pelot D. Hepatic enzyme elevations associated with baclofen. Clin Pharm 1984; 3: 196-7. PubMed PMID: 6723229.

(Manufacturer reported than <1% of patients on baclofen developed AST elevations, but no case of overt hepatitis was reported; one patient with traumatic quadriplegia and spasticity developed ALT elevations [414 U/L] after 6 weeks of escalating doses of baclofen [80 mg/day] without symptoms or jaundice, which fell to normal with decrease in dose).

Dapas F, Hartman SF, Martinez L, et al. Baclofen for the treatment of acute low-back syndrome. A double-blind comparison with placebo. Spine 1985; 10: 345-9. PubMed PMID: 2931831.

(Placebo controlled trial in 200 patients, 98 on baclofen for 6 weeks; no mention of hepatotoxicity).

Garabedian-Ruffalo SM, Ruffalo RL. Adverse effects secondary to baclofen withdrawal. Drug Intell Clin Pharm 1985; 19: 304-6. PubMed PMID: 3050930.

(40 year old woman with multiple sclerosis developed spasms and acute psychosis within days of switching from baclofen to amitriptyline; no mention of hepatotoxicity).

Hulme A, MacLennan WJ, Ritchie RT, John VA, Shotton PA. Baclofen in the elderly stroke patient its side-effects and pharmacokinetics. Eur J Clin Pharmacol 1985; 29: 467-9. PubMed PMID: 3912190.

(12 elderly patients given baclofen had higher drug levels and more problems with drowsiness, but no mention of hepatotoxicity).

Roussan M, Terrence C, Fromm G. Baclofen versus diazepam for the treatment of spasticity and long-term follow-up of baclofen therapy. Pharmatherapeutica 1985; 4: 278-84. PubMed PMID: 3906673.

(18 patients were treated with baclofen for 4 years; authors make no mention of hepatotoxicity).

Stien R, Nordal HJ, Oftedal SI, Sletteb M. The treatment of spasticity in multiple sclerosis: a double-blind clinical trial of a new anti-spastic drug tizanidine compared with baclofen. Acta Neurol Scand 1987; 75: 190-4. PubMed PMID: 3554879.

(40 patients given either tizanidine or baclofen for 6 weeks, no changes observed in laboratory tests of liver function or mention made of hepatotoxicity of either drug).

Bass B, Weinshenker B, Rice GP, et al. Tizanidine versus baclofen in the treatment of spasticity in patients with multiple sclerosis. Can J Neurol Sci 1988; 15: 15-9. PubMed PMID: 3345456.

(Double-blind cross over study of tizanidine vs baclofen for 5 weeks each and routine laboratory monitoring found no alterations in biochemical test results with either agent).

Hoogstraten MC, van der Ploeg RJ, vd Burg W, Vreeling A, van Marle S, Minderhoud JM. Tizanidine versus baclofen in the treatment of spasticity in multiple sclerosis patients. Acta Neurol Scand 1988; 77: 224-30. PubMed PMID: 3376747.

(16 patients treated with tizanidine and baclofen in a cross over study; muscle weakness was more common with baclofen; no mention of laboratory tests or hepatotoxicity).

Nance PW. A comparison of clonidine, cyproheptadine and baclofen in spastic spinal cord injured patients. J Am Paraplegia Soc 1994; 17: 150-6. PubMed PMID: 7964712.

(No mention of hepatotoxicity).

Chen KS, Bullard MJ, Chien YY, Lee SY. Baclofen toxicity in patients with severely impaired renal function. Ann Pharmacother 1997; 31: 1315-20. PubMed PMID: 9391686.

(Total of 16 instances of baclofen toxicity with depressed consciousness in patients on renal dialysis; no mention of hepatotoxicity).

Groves L, Shellenberger MK, Davis CS. Tizanidine treatment of spasticity: a meta-analysis of controlled, double-blind, comparative studies with baclofen and diazepam. Adv Ther 1998; 15: 241-51. PubMed PMID: 10186943.

(Metaanalysis of 10 trials in 270 patients comparing baclofen and tizanidine reported global tolerance, but no mention made of ALT abnormalities or hepatotoxicity).

Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage 2004; 28: 140-75. PubMed PMID: 15276195.

(Thorough review of the pharmacology, efficacy and side effects of the muscle relaxants).

Russo MW, Galanko JA, Shrestha R, Fried MW, Watkins P. Liver transplantation for acute liver failure from drug-induced liver injury in the United States. Liver Transpl 2004; 10:1018-23. (Among PubMed PMID: 15390328.

~50,000 liver transplants done in the US between 1990 and 2002, 270 [0.5%] were done for drug induced acute liver failure, but none were attributed to a specific muscle relaxant).

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, one was attributed to chlorzoxazone, but none to baclofen).

Caruso A, Vecchio R, Patti F, Neri S. Drug rash with eosinophilia and systemic signs syndrome in a patient with multiple sclerosis. Clinical Therapeutics 2009; 31: 580-4. PubMed PMID: 19393848.

(44 year old woman developed drug rash, eosinophilia and jaundice 8 weeks after starting baclofen, mitoxantrone, and piracetam [bilirubin 19.3 mg/dL, ALT 561 U/L, Alk P 705 U/L], resolving within 6 months of stopping; causality assessment implicated mitoxantrone [a toposiomerase inhibitor used to treat multiple sclerosis]).

Addolorato G, Leggio L. Safety and efficacy of baclofen in the treatment of alcohol-dependent patients. Curr Pharm Des 2010; 16: 2113-7. PubMed PMID: 20482507.

(Review of trials of baclofen for alcohol withdrawal and dependence; in large numbers of patients with chronic alcoholism and some with significant alcoholic liver disease, baclofen "did not produce any serious or severe side effects").

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, none of which were attributed to baclofen or other muscle relaxants).

Garbutt JC, Kampov-Polevoy AB, Gallop R, Kalka-Juhl L, Flannery BA. Efficacy and safety of baclofen for alcohol dependence: a randomized, double-blind, placebo-controlled trial. Alcohol Clin Exp Res 2010; 34: 1849-57. PubMed PMID: 20662805.

(Controlled trial of 12 weeks of baclofen vs placebo in 80 patients with alcohol dependence reported that adverse events were "relatively mild"; no mention of ALT elevations or hepatotoxicity).

Heydtmann M. Baclofen effect related to liver damage. Alcohol Clin Exp Res 2011; 35: 848. PubMed PMID: 21303383.

(Letter in response to Garbutt [2010] describing baclofen treatment of 50 patients with alcohol dependence found that those with advanced liver disease responded to lower doses than those with normal liver function).

Macaigne G, Champagnon N, Harnois F, Cheiab S, Chayette C. Baclofen-induced acute hepatitis in alcohol-dependent patient. Clin Res Hepatol Gastroenterol 2011; 35: 420-1. PubMed PMID: 21561828.

(46 year old woman with chronic alcoholism and abnormal serum enzymes had worsening of ALT [1.5 to 6.5 times ULN], AST [5.5 to 9 times ULN], with no change in bilirubin or Alk P 2 months after starting baclofen, improving on stopping).

Brennan JL, Leung JG, Gagliardi JP, Rivelli SK, Muzyk AJ. Clinical effectiveness of baclofen for the treatment of alcohol dependence: a review. Clin Pharmacol 2013; 5: 99-107. PubMed PMID: 23869179.

(Review of 4 randomized controlled trials of baclofen for alcohol dependence found that data in support of its efficacy were mixed, but that data were consistent regarding its safety; no discussion of ALT elevations or hepatotoxicity).

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: 1340-1352.e7. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 5 cases [0.7%] were attributed to muscle relaxants, one of which due to baclofen).