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Flavocoxid

Updated: January 30, 2018.

OVERVIEW

Introduction

Flavocoxid is a medical food consisting of plant derived flavonoids which have antiinflammatory activity and are used to treat chronic osteoarthritis. Flavocoxid has been linked to minor elevations in serum enzyme levels during therapy and to rare instances of clinically apparent liver injury.

Background

Flavocoxid (flay" voe kox' id) is a proprietary blend of purified plant derived bioflavonoids including baicalin and catechins. Flavocoxid inhibits cyclooxygenases (both Cox-1 and Cox-2) as well as lipoxygenases (5-Lox) in vitro and in animal models, which may account for its antiinflammatory and antioxidant activity. Flavocoxid inhibits the conversion of arachidonic acid to reactive prostaglandins and reduces the levels of these inflammatory mediators in synovial fluid. Flavocoxid was approved for use as a medical food in the United States in 2004. However, this approval was withdrawn in December 2017 and it is not longer available as an FDA approved medical food. It was previously available by prescription for use in chronic osteoarthritis in tablets of 500 mg under the commercial name Limbrel. The typical dose was 500 mg twice daily. Side effects were not common and were similar in frequency to those experienced by patients on placebo.

Hepatotoxicity

In premarketing clinical trials, serum aminotransferase elevations occurred in up to 10% of patients on flavocoxid therapy, but elevations above 3 times the upper limit of normal occurred in only 1% to 2% of recipients. Since its release, however, there have been several reports of clinically apparent acute liver injury attributed to flavocoxid. Most cases have occurred in women, who perhaps are more likely to use flavocoxid. The time to onset was 1 to 5 months, and the pattern of enzyme elevations was usually hepatocellular or mixed. Most cases were moderate in severity and no instance of acute liver failure or death has been reported. Resolution upon stopping flavocoxid occurred in 1 to 3 months. Immunoallergic features were present in some patients, but were mild and autoantibodies were not common. At least one instance of recurrence upon rechallenge has been reported.

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

Mechanism of Injury

Flavocoxid is a proprietary mixture of plants and herbs and it is unclear which component(s) might be responsible for liver injury. The mixture includes extracts from Scutellaria baicalensis (skullcap, containing the

phytochemical baicalin) and Acacia catechu (catechin), both of which have been implicated in causing rare instances of idiosyncratic acute liver injury, but the mechanism is unknown.

Outcome and Management

No instances of acute liver failure or chronic liver injury have been linked to flavocoxid use and all cases have been self-limited, without subsequent chronic hepatitis or vanishing bile duct syndrome. Recurrence upon reexposure has been reported and rechallenge should be avoided. There is no information on possible cross sensitivity of hepatic injury with other medications or herbal agents such as skull cap or green tea.

Drug Class: Herbal and Dietary Supplements; Antirheumatic Agents

CASE REPORT

Case 1. Acute hepatitis with jaundice after flavocoxid therapy.

[Modified from Case 1: Chalasani N, Vuppalanchi R, Navarro V, Fontana R, Bonkovsky H, Barnhart H, Kleiner DE, Hoofnagle JH. Acute liver injury due to flavocoxid (Limbrel), a medical food for osteoarthritis: a case series. Ann Intern Med 2012; 156: 857-60, W297-300. PubMed Citation]

A 58 year old woman developed jaundice 10 weeks after starting flavocoxid (500 mg twice daily) for osteoarthritis. She had no history of liver disease, risk factors for viral hepatitis and did not drink alcohol. Other medications included aspirin, tramadol, omeprazole, ezetimibe, zolpidem, glucosamine, calcium, flaxseed oil and vitamins, all of which she had taken chronically. Physical examination was largely unremarkable, but her laboratory tests showed elevations in serum bilirubin (2.5 mg/dL), ALT (1105 U/L), AST (1198 U/L) and alkaline phosphatase (487 U/L) (Table). There was no eosinophilia and the prothrombin time was normal. Liver tests had been normal on several occasions in the past. Flavocoxid was discontinued, but over the next week she became jaundiced (peak bilirubin 7.3 mg/dL) and serum enzyme levels remained elevated. Tests for hepatitis A, B, C and E were negative as were autoantibodies. Ultrasound of the abdomen showed no evidence of biliary obstruction or hepatic masses. A liver biopsy showed a moderately severe, acute lobular hepatitis with portal inflammation (including eosinophils) without evidence of chronic liver disease or fibrosis. Two weeks after stopping flavocoxid she began to improve. Symptoms resolved within a month and all liver tests were normal when she was seen 3 months after onset. Flavocoxid was not restarted.

Key Points

Medication:	Flavocoxid (500 mg twice daily)
Pattern:	Hepatocellular (R=5.9)
Severity:	3+ (jaundice, hospitalization)
Latency:	3 months
Recovery:	3 months
Other medications:	Aspirin, tramadol, omeprazole, ezetimibe, zolpidem, glucosamine, calcium, flaxseed oil and vitamins

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre	Pre	23	109	0.6	
3 months	0	1105	487	2.5	Admission
	4 days	1259	530	3.4	

Table continued from previous page.

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
	10 days	1540	525	7.3	Liver biopsy
	16 days	1195	433	3.9	
4 months	26 days	431	218	2.1	
	30 days	298	215	1.3	Asymptomatic
	5 weeks	97	151	0.8	
5 months	6 weeks	42	124	0.8	
6 months	12 weeks	11	117	0.5	
9 months	24 weeks	14	89	0.2	
Normal Values		**<42**	**<105**	**<1.2**	

Comment

A 58 year old woman suffered a moderate case of acute liver injury with a hepatocellular pattern of serum enzyme elevations arising after three months of flavocoxid therapy. A liver biopsy suggested drug induced liver injury, and no other obvious cause of acute hepatitis was identified. The serum ALT and AST were in the typical range for acute viral hepatitis, but the prominent elevation in alkaline phosphatase suggested a somewhat “mixed” pattern, which is more typical of drug induced liver injury. Flavocoxid is a medical food and regulated more as a nutritional supplement than a drug. Medical foods can be prescribed for specific indications (such as osteoarthritis), but have not undergone the rigorous proof of efficacy and safety that are required of medications. They are "generally recognized as safe" by the FDA. Flavocoxid, however, has recently been withdrawn, more likely due to questions of efficacy rather than safety.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Flavocoxid – Limbrel®

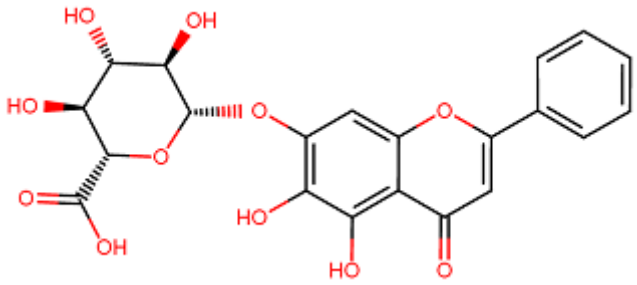
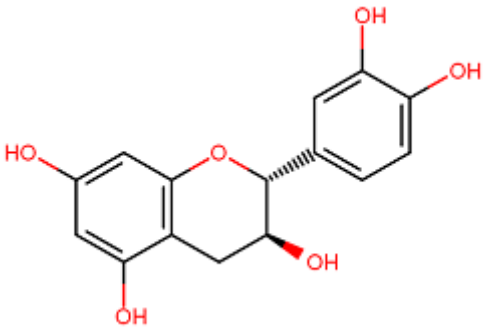
DRUG CLASS

Herbal and Dietary Supplements

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Baicalin	21967-41-9	C21-H18-O11	
Catechin	154-23-4	C15-H14-O6	

ANNOTATED BIBLIOGRAPHY

References updated: 30 January 2018

Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. The NSAIDS. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 517-41.

(Review of hepatotoxicity of NSAIDs published in 1999, discusses hepatotoxicity of NSAIDs, but does not specifically mention flavocoxid).

Lewis JH, Stine JG. Nonsteroidal anti-inflammatory drugs and leukotriene receptor antagonists. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 369-401. (Review of hepatotoxicity of NSAIDs;

flavocoxid is not mentioned).

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, none were attributed to flavocoxid).

Morgan SL, Baggott JE, Moreland L, Desmond R, Kendrach AC. The safety of flavocoxid, a medical food, in the dietary management of knee osteoarthritis. J Med Food 2009; 12: 1143-8. PubMed PMID: 19857081.

(Among 59 patients with osteoarthritis treated with placebo or flavocoxid for 12 weeks, side effects were mild and similar to placebo, with no overall differences in serum aminotransferase levels).

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, but none to flavocoxid).

Levy RM, Khokhlov A, Kopenkin S, Bart B, Ermolova T, Kantemirova R, Mazurov V, et al. Efficacy and safety of flavocoxid, a novel therapeutic, compared with naproxen: a randomized multicenter controlled trial in subjects with osteoarthritis of the knee. Adv Ther 2010; 27: 731-42. PubMed PMID: 20845002.

(Controlled trial of 12 week course of flavocoxid versus naproxen in 220 patients with osteoarthritis found similar rates of ALT elevations, and no patient had clinically apparent hepatitis or an ALT level >5 times ULN).

Pillai L, Burnett BP, Levy RM; GOAL Study Cooperative Group. GOAL: multicenter, open-label, post-marketing study of flavocoxid, a novel dual pathway inhibitor anti-inflammatory agent of botanical origin. Curr Med Res Opin 2010; 26: 1055-63. PubMed PMID: 20225990.

(Among 1005 patients with osteoarthritis treated with flavocoxid in an open label study, liver test abnormalities occurred in only one [0.1%], but no details given).

Levy RM. Flavocoxid and hypersensitivity pneumonitis. Chest 2011; 140: 827-8; author reply 828. PubMed PMID: 21896531.

(Letter mentions that among an estimated 270,000 persons treated with flavocoxid since its marketing in 2004, 3 cases of drug induced hypersensitivity pneumonitis were reported to the sponsor).

Product information. Limbrel. 2011.

(The product sponsor mentions that liver test abnormalities were found in less than 10% of patients treated with flavocoxid, but that levels of 3-5 times ULN occurred in less than 2% and that there were rare instances of hepatitis [n=3] and jaundice [n=6] that were self-limited and resolved rapidly with stopping).

Chalasani N, Vuppalanchi R, Navarro V, Fontana R, Bonkovsky H, Barnhart H, Kleiner DE, Hoofnagle JH. Acute liver injury due to flavocoxid(Limbrel), a medical food for osteoarthritis: a case series. Ann Intern Med 2012; 156: 857-60, W297-300. PubMed PMID: 22711078.

(Four women, ages 57 to 68 years, developed jaundice 1-3 months after starting flavocoxid [peak bilirubin 2.0 to 20.8 mg/dL, ALT 741 to 1540 U/L, Alk P 286 to 770 U/L], resolving in 1 to 3 months: Case 1).

Reichenbach S, Jüni P. Medical food and food supplements: not always as safe as generally assumed. Ann Intern Med 2012; 156: 894-5, W314. PubMed PMID: 22711083.

(Editorial in response to Chalasani [2012] discussing the potential of herbals and medical foods for causing adverse events and the need for better regulation and monitoring of their use).

Available at: https://www.fda.gov/safety/recalls/ucm594357.htm

(News report on the voluntary nationwide recall of flavocoxid due to rare, but serious adverse events including liver enzyme elevations and hepatitis).

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