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Salsalate

Updated: December 20, 2013.

OVERVIEW

Introduction

Salsalate is a nonacetylated dimer of salicylic acid that is used in the treatment of chronic arthritis as an analgesic and antipyretic. Salsalate can cause moderate serum aminotransferase elevations when given in high doses in a manner similar to aspirin.

Background

Salsalate (sal' sa late) is a dimer of salicylic acid that has antiinflammatory, analgesic and antipyretic actions similar to aspirin. The antiinflammatory and analgesic effects of salsalate are probably mediated by inhibition of prostaglandin synthesis. Although available for several decades, salsalate is not commonly used. Current indications include treatment of chronic arthritis due to osteoarthritis or rheumatoid arthritis. Salsalate is also used for minor to moderate pain. Salsalate is available as tablets of 500 and 750 mg in multiple generic forms and previously under the brand name of Disalcid. The recommended regimen is 750 to 1500 mg twice daily, based upon response and tolerance. Common side effects are intestinal upset, nausea, headache, somnolence, dizziness, and tinnitus.

Hepatotoxicity

Prospective studies show that a proportion of patients taking salsalate experience at least transient serum aminotransferase elevations particularly when it is given in higher doses. These abnormalities may resolve even with drug continuation or after dose reduction. Marked aminotransferase elevations (>10 fold elevated) occur rarely except with use of higher doses (3 g daily or more) in a manner similar to aspirin. Clinically apparent liver injury with jaundice from salsalate has not been reported and must be very rare. Salsalate is probably capable of inducing Reye syndrome in a susceptible child or adolescent and, like aspirin, should be avoided in those age groups.

Mechanism of Injury

The mechanism of salsalate hepatotoxicity is likely a direct cytotoxic effect of high doses, similar to that of aspirin.

Outcome and Management

Salsalate hepatotoxicity has been marked by aminotransferase elevations without jaundice. Some patients have nonspecific symptoms or gastrointestinal upset. There have been no reported cases of acute hepatitis, acute liver

failure or vanishing bile duct syndrome related to salsalate. Aminotransferase elevations during therapy can often be managed by dose adjustment.

Drug Class: Salicylates

Other Drugs in the Class: Aspirin, Diflunisal, Trisalicylate

CASE REPORT

Case 1. Acute enzyme elevations due to high dose salsalate therapy.

[Modified from a case in the database of the Drug-Induced Liver Injury Network]

A 27 year old man with HIV infection was enrolled in an experimental study of the effects of salsalate on endothelial cell function. He was without symptoms of HIV infection or liver disease, was not receiving antiretroviral therapy and had normal baseline liver tests (Table). He was started on salsalate (750 mg orally twice daily) and monitored closely. After 10 days he developed nausea and abdominal pain and salsalate was stopped. He had no previous history of liver disease, alcohol abuse or drug allergies. He had been taking weekly prophylatic sulfamethoxazole/trimethoprim for several months. Physical examination was unrevealing. Serum enzymes were markedly elevated [ALT 1101 U/L, AST 532 U/L, Alk P 77 U/L, bilirubin normal]. The while blood cell count was normal with 1% eosinophils. The INR was 1.0. He tested positive for anti-HBs and anti-HBc without HBsAg. Tests for hepatitis A and C were negative. He had low levels of serum autoantibodies (ANA 1:40, SMA 1:80), but globulin levels were normal (albumin 4.3 g/L, globulins 2.9 g/dL). His symptoms resolved within days of stopping salsalate and serum enzymes were normal three weeks later.

Key Points

Medication:	Salsalate (1.5 grams daily)
Pattern:	Hepatocellular (R= 40)
Severity:	1+ (enzyme elevations without jaundice)
Latency:	10 days
Recovery:	Rapid (19 days)
Other medications:	Sulfamethoxazole/Trimethoprim

Laboratory Values

Days After Starting	Days After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Pre		21	61	0.9	
0		33	52	1.2	
10	0	1101	77	0.9	Nausea
17	7	207	79	0.8	Asymptomatic
29	13	38	67	0.7	
6 months	6 months	54	67	0.9	
Normal Values		**<45**	**<95**	**<1.2**	

Comment

A very convincing case of salsalate induced hepatotoxicity. The onset was within a few days of starting the drug. The patient was mildly symptomatic, but not jaundiced. There were no changes in alkaline phosphatase or

bilirubin levels. Recovery was rapid once salsalate was stopped, and there were no other obvious causes of liver injury. The clinical phenotype was acute hepatic necrosis rather than hepatitis. The dose of salsalate was lower than that usually associated with serum aminotransferase elevations, suggesting an element of increased susceptibility to this injury.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Salsalate – Generic, Disalcid® (not available in US)

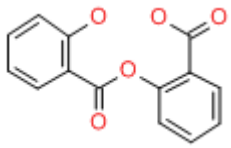
DRUG CLASS

Antiinflammatory Agents

COMPLETE LABELING (not available)

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO	MOLECULAR FORMULA	STRUCTURE
Salsalate	552-94-3	C14-H10-O5	

ANNOTATED BIBLIOGRAPHY

References updated: 20 December 2013

Zimmerman HJ. Drugs used to treat rheumatic and musculospastic disease. Chapter 19: The NSAIDS. In Zimmerman, HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott Williams & Williams, 1999, pp. 517-41.

(Review of hepatotoxicity of salicylates published in 1999, discusses aspirin but not salsalate specifically).

Lewis JH, Stine JG. Nonsteroidal anti-inflammatory drugs and leukotriene receptor antagonists. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd Edition. Amsterdam: Elsevier, 2013. pp. 370-402. *(Expert review of liver injury caused by NSAIDs mentions that*

salsalate can cause aminotransferase elevations).

Grossner T, Smyth EM, Fitzgerald GA. Anti-inflammatory, antipyretic, and analgesic agents: pharmacotherapy of gout. In, Brunton LL, Chabner BA, Knollman BC. Goodman & Gilman's The pharmacological basis of therapeutics, 12th ed. New York: McGraw-Hill, 2011. p. 959-1004.

(Textbook of pharmacology and therapeutics).

Juluri R, Gupta S, Vuppalanchi R. Serum concentration-dependent hepatotoxicity in individuals receiving oral salsalate. Dig Dis Sci 2009: 54: 1375-6. 18770032. PubMed PMID: 18770032.

(Prospective study in 11 patients with HIV infection given 1500 mg salsalate twice daily for 8 weeks; 4 patients developed ALT elevations [mean=27 rising to 482 and later to 116 U/L], 2 had symptoms, all resolved rapidly with stopping).

Goldfine AB, Fonseca V, Jablonski KA, Pyle L, Staten MA, Shoelson SE; TINSAL-T2D (Targeting Inflammation Using Salsalate in Type 2 Diabetes) Study Team. The effects of salsalate on glycemic control in patients with type 2 diabetes: a randomized trial. Ann Intern Med 2010; 152: 346-57. PubMed PMID: 20231565.

(Controlled trial of 14 weeks of 3-4 g of salsalate daily vs placebo in 54 patients with diabetes found decreases in serum HgA1c and glucose, but no change in serum ALT, AST or GGT; dose limiting side effect was tinnitus).

Hileman CO, Carman TL, Gripshover BM, O'Riordan M, Storer NJ, Harrill DE, White CA, McComsey GA. Salsalate is poorly tolerated and fails to improve endothelial function in virologically suppressed HIV-infected adults. AIDS 2010; 24: 1958-61. PubMed PMID: 20613460.

(Open label study of 13 weeks of salsalate [4 g daily] vs no treatment in 40 patients with HIV infection on antiretroviral therapy found no effect on markers of inflammation and poor tolerance, with minor [<3 times ULN] ALT elevations in 6 [30%]).

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, salsalate was implicated in one patient who developed marked ALT elevations without jaundice [bilirubin 0.9 mg/dL, ALT 1101 U/L, Alk P 77 U/L] 10 days after starting salsalate [1.5 g daily], resolving within 3 weeks of stopping: Case 1).