Original Article

Unexpected cutaneous reactions in diabetic and prediabetic patients treated with salsalate

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ABSTRACT

Objective: The most commonly reported side effects of salsalate are gastrointestinal events, and few reports are available on its cutaneous side effects. We therefore assessed cutaneous side effects among diabetic/pre-diabetic patients treated with salsalate.

Methodology: In a randomized placebo-controlled trial, we evaluated cutaneous side effects in 52 diabetic and 124 pre-diabetic patients, 90 of whom received 3 g/day salsalate and 86 of whom receive a placebo for four weeks. The evaluation was carried out every week using a checklist completed by a single general practitioner.

Results: The difference between the salsalate- and placebo-treated groups in overall prevalence of cutaneous reactions was not significant (26.7% versus 17.4%; $P < 0.05$). Side effects included urticaria (nine (10.1%) salsalate-treated versus six (6.9%) placebo-treated), rashes (five (5.5%) salsalate-treated versus three (3.4%) placebo-treated), pruritus (six (6.7%) salsalate-treated versus three (3.4%) placebo-treated), and edema (two (2.2%) salsalate-treated versus one (1.2%) placebo-treated); in addition, one (1.1%) case of erythema nodosum and one (1.1%) of vasculitis were observed in the salsalate-treated group. In the salsalate group, therapy was discontinued by the physician for three (3.3%) patients because of acute and severe vasculitis, erythema nodosum and urticaria and two (2.2%) patients stopped the treatment themselves because of mild urticaria compared with two patients who stopped using the placebo.

Conclusions: Salsalate can cause several and, in some cases, severe cutaneous side effects in patients with diabetes/pre-diabetes. Because these cutaneous eruptions can raise various concerns, including patient non-compliance, greater attention should be paid to dermatological problems in patients under salsalate treatment.

KEY WORDS: Salsalate, Cutaneous, Side effects, Diabetes.

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INTRODUCTION

Salsalate, the non-acetylated form of salicylate, is a non-steroidal analgesic and anti-inflammatory agent that is used in the treatment of rheumatoid arthritis, osteoarthritis and related rheumatic disorders.[1] Recent studies have shown that salsalate can reduce insulin resistance.[2,3] and facilitates recovery from vascular injury[4], probably via its anti-inflammatory effects. It inhibits cyclooxygenase enzymes, which results in reduced production of prostaglandin precursors.[5,6] Other actions, the mechanisms of which have not been completely explained, include neutrophil activation, inhibition and reduction of

Table-I: Demographic data.

	Salsalate	*Placebo*	*P value*
Number of patients	90	86	
Mean age(years)	47.64(SD* = 7.78)	48.65(SD = 7.76)	
Sex (%)	Male = 18(20%)	Female = 72(80%)	Male = 22(25.6%) Female = 64(74.4%)

chemotaxis, modification of lymphocyte activity, a decrease in blood free fatty acids, and an increase in the level of anti-inflammatory cytokines.[7-9] Accordingly, a growing number of trials have been conducted on salsalate as a potential anti-diabetic therapy [21938543, 21617098, 21225023, 20516365].

Despite several beneficial effects, various adverse reactions to salsalate have been reported, the most common of which are gastrointestinal effects such as nausea, heartburn, and dyspepsia in more than 10% of cases, and others such as drowsiness, gastrointestinal ulceration, hemolytic anemia, weakness, dyspnea, rash and anaphylactic shock in less than 10% of cases.[6]

One study reported a lichenoid eruption following one month of salsalate therapy[10], and lingual lesions have been reported after prolonged exposure to salsalate.[11] Because of the absence of data regarding the cutaneous side effects of salsalate, the aim of the present study was to assess such side effects, and also to report two complicated adverse reactions that had not been reported previously: erythema nodosum and vasculitis.

METHODOLOGY

Pre-diabetic (n = 124) and diabetic patients (n = 52) who had taken part in a placebo-controlled trial of salsalate therapy for the control of blood sugar[12] were included in this study. Briefly, the trial comprised treatment with salsalate (3 g/day) or placebo for 12 weeks. Patients with a history of hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs), asthma, class III/IV heart failure, cirrhosis, consistent steroid use, leukopenia, or thrombocytopenia were excluded from the trial (for further information see[12]).

Patients were visited by a single general practitioner to screen for side effects, and were then referred to a single dermatologist who was familiar with NSAIDs side effects to distinguish the types of eruption. The general practitioner and dermatologist were blinded with regard to salsalate and placebo treatments. Other information collected included sex, age, drug history, and fatty liver evaluated by ultrasonography. The data were analyzed by univariate and multivariate (multiple logistic regression) methods using SPSS statistical package version 18.0; a P-value of less than 0.05 was considered to be significant.

RESULTS

Details of the trial results were presented in a recently published report.[12] The demographic characteristics of the patients are shown in Table-I. The difference between the salsalate- and placebo-treated groups regarding overall frequency of dermatological side effects was not statistically significant (26.7% versus 16.3%; $P < 0.05$). In the salsalate group, therapy was discontinued for three patients because of severe cutaneous side effects, and two patients stopped taking the treatment because of mild urticaria. In the placebo group, two patients stopped using the drug because of cutaneous irritations. Details of dermatological side effects in the two groups are presented in Table-II.

Urticaria, described as well-defined pruritic wheals and flares, was remarkable in one female patient after 15 days of salsalate treatment. She had a history of anaphylactic shock for reasons unknown. Salsalate was discontinued directly and corticosteroid treatment (25 mg/day) was initiated and gradually reduced within two weeks. Erythema nodosum, described as tender erythematous nodular lesions, developed on the anterior surfaces of the legs of another female patient during the 3rd week of treatment with salsalate. The diagnosis (polymorphonuclear cell predominant septal panniculitis) was confirmed by an incisional

Table-II: Fitting logistic regression on eruption.

	P-value	*Odds ratio*	*95% C.I. for EXP(B)*	
			Lower	*Upper*
Sex (male = 0 female = 1)	0.567	1.425	0.424	4.793
Age	0.096	1.064	0.989	1.146
Fatty liver*	0.707	1.233	0.414	3.677
Polypharmacy**	0.002	4.441	1.710	11.530
Salsalate	0.001	7.365	2.175	24.933

*Diagnosed with liver ultrasonography
**using more than two drugs for more than 6 months

Table-III: Distribution of dermatological side effects.

	Urticaria	*Macula popular Rashes*	*Puritus*	*Edema*	*Puritus & edema*	*Other*	*Total*
Salsalate (%) n = 90	9(10%)	5(5.5%)	6(6.7%)	2(2.2%)	0	2(2.2%)	24(26.7%)
Placebo (%) n = 86	6(7%)	3(3.5%)	3(3.5%)	1(1.2%)	2(2.3%)	0	15(17.4%)

biopsy. In this patient, salsalate treatment was stopped and, after 10 days of indomethacin (25 mg TDS) treatment, the rash disappeared. One female patient developed erythematous purpuric lesions on the lower leg after one week of salsalate treatment, and a diagnosis of polymorphonuclear cell predominant leukocytoclastic vasculitis was confirmed by biopsy. Salsalate was stopped and prednisolone treatment (25 mg/day) was initiated, then gradually reduced and within 10 days the lesions had completely disappeared.

A multivariate logistic regression analysis of the eruptions was made taking different factors that might affect side effects into account. Logistic regression including sex, age, fatty liver, and polypharmacy showed that the eruption rate was significantly higher in patients who received salsalate than in those who received the placebo (odds ratio = 7.365; 95% confidence interval = 2.175–24.933; P = 0.001).

DISCUSSION

The aim of this study was to assess the cutaneous side effects of salsalate. We found that salsalate can cause several and, in some cases, severe cutaneous side effects, which were similar to those caused by other NSAIDs. Rare side effects of NSAIDs have been reported to be Stevens-Johnson syndrome, erythema multiforme or toxic epidermal necrolysis. Common cutaneous reactions include pruritus, morbilliform rashes, urticaria and photosensitivity, of which urticaria is the most frequent. According to previous reports, purpura and vasculitis are uncommon reactions that can be attributed to NSAIDs.[13,14] We found one case of vasculitis and one case erythema nodosum as well as urticaria, rashes, pruritus and edema. To the best of our knowledge, vasculitis and erythema nodosum due to treatment with salsalate have not been reported previously. Our study was carried out among Asian diabetic and pre-diabetic patients, and the severity of the drug reactions may be due to the ethnicity of our study population. Because of polymorphisms in cytochrome P450 (CYP) enzymes, drug metabolism and drug reactions vary among different populations[15,16], and liver metabolism is slower in Iranians due to fewer metabolizing enzymes such as CYP2C9 and CYP2C19.[17]

A suggested mechanism of NSAIDs hypersensitivity is the activation of mast cells mediated by immunoglobulin (Ig) E- and non-IgE-dependent pathways.[18] The most common IgE-dependent activation of mast cells caused by NSAIDs is urticaria.[13] Other non-IgE-dependent mechanisms that have been described for NSAIDs include cutaneous pseudoallergic urticaria. Because mast cells first need to be sensitized, IgE-dependent reactions do not commonly occur after the first dose of a drug. Our patients did not show acute reactions after the first dose of salsalate and it therefore appears that the dominant mechanism for rashes, urticaria, erythema nodosum and vasculitis may be IgE-dependent.

Salsalate causes less fecal gastrointestinal blood loss than aspirin and other NSAIDs[19], and is also used in the treatment of arthritis, metabolic and vascular disorders, and diabetes[3,12,20,21] With regard to the irritable cutaneous reactions that salsalate can cause in intolerant patients, it has been suggested that more attention be paid to its side effects, especially in high-risk groups including those with a history of hypersensitivity to NSAIDs, liver dysfunction, and polypharmacy, and older patients.[22,23] Guidelines on oral provocation or skin tests to evaluate hypersensitivity in patients with a history of reactions to a single dose of NSAIDs could be helpful in this regard.

CONCLUSIONS

The results of our study showed that salsalate can cause several and, in some cases, severe cutaneous side effects in patients with diabetes/pre-diabetes. Since these cutaneous eruptions can raise various concerns including patient non-compliance, greater attention should be paid to dermatological problems in patients under salsalate treatment. Because insufficient studies have been carried out to establish specifically the side effects of salsalate, more double-blinded trials with larger sample sizes and longer follow-ups are recommended to determine the exact features and severity of the reactions to this drug.

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REFERENCES

1. Fleischman, A., et al., Salsalate improves glycemia and inflammatory parameters in obese young adults. Diabetes Care 2008;31(2):289.
2. Chai, W., et al., Salsalate Attenuates Free Fatty Acid-Induced Microvascular and Metabolic Insulin Resistance in Humans. Diabetes Care, 2011.
3. Desouza, C.V., An overview of salsalate as a potential antidiabetic therapy. Drugs Today (Barc), 2010;46(11):847-853.
4. Murthy, S.N., et al., Effects of salsalate therapy on recovery from vascular injury in female Zucker fatty rats. Diabetes 2010;59(12):3240-3246.
5. Goldfine, A.B., et al., Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. Clinical and translational science 2008;1(1):36-43.
6. UpToDate, ed. D.S. Basow, Waltham: UpToDate.
7. Ali, A.T.M.M., J.M. Hanson, and J. Morley, Effects of non-steroidal anti-inflammatory drugs on lymphocyte activation. Inflammation Research 1984;14(2):216-222.
8. Altman, R. Neutrophil activation: an alternative to prostaglandin inhibition as the mechanism of action for NSAIDs. 1990.
9. Atkinson, M.H., H.A. Ménard, and G.H. Kalish, Assessment of salsalate, a nonacetylated salicylate, in the treatment of patients with arthritis. Clinical therapeutics 1995;17(5):827-837.
10. Powell, M.L., A. Ehrlich, and D.V. Belsito, Lichenoid drug eruption to salsalate. J Am Acad Dermatol 2001;45(4):616-619.
11. Ruscin, J.M. and J.D. D'Astroth, Lingual lesions secondary to prolonged contact with salsalate tablets. Ann Pharmacother 1998;32(11):1248.
12. Faghihimani, E., et al., Salsalate improves glycemic control in patients with newly diagnosed type 2 diabetes. Acta Diabetol 2011;49(2):1-5.
13. Sanchez-Borges, M., A. Capriles-Hulett, and F. Caballero-Fonseca, Cutaneous reactions to aspirin and nonsteroidal antiinflammatory drugs. Clin Rev Allergy Immunol 2003;24(2):125-136.
14. Roujeau, J.C., Clinical aspects of skin reactions to NSAIDs. Scand J Rheumatol Suppl 1987;65:131-134.
15. Lynch, T. and A. Price, The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. Am Fam Physician 2007;76(3):391-396.
16. Zand, N., et al., Genetic polymorphisms of cytochrome P450 enzymes 2C9 and 2C19 in a healthy Iranian population. Clin Exp Pharmacol Physiol 2007;34(1-2):102-105.
17. Stevenson, D.D., Aspirin and NSAID sensitivity. Immunol Allergy Clin North Am 2004;24(3):491-505.
18. Cohen, A., Fecal blood loss and plasma salicylate study of salicylsalicylic acid and aspirin. J Clin Pharmacol 1979;19(4):242-247.
19. McCarty, M.F., Salsalate may have broad utility in the prevention and treatment of vascular disorders and the metabolic syndrome. Med Hypotheses 2010;75(3):276-281.
20. Atkinson, M.H., H.A. Menard, and G.H. Kalish, Assessment of salsalate, a nonacetylated salicylate, in the treatment of patients with arthritis. Clin Ther 1995;17(5):827-837.
21. Merrell, M.D. and N.J. Cherrington, Drug metabolism alterations in nonalcoholic fatty liver disease. Drug Metab Rev 2011;43(3):317-334.
22. Hajjar, E.R., et al., Adverse drug reaction risk factors in older outpatients. Am J Geriatr Pharmacother 2003;1(2):82-89.
23. Sanchez-Borges, M., NSAID hypersensitivity (respiratory, cutaneous, and generalized anaphylactic symptoms). Med Clin North Am 2010;94(4):853-864.