

Chronic rhinosinusitis: Potential new use for topical sulfasalazine

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Clinical Implication

- A topical nasosinus rinse that contained sulfasalazine may be a safe and effective treatment for some patients with chronic rhinosinusitis, even if disease is resistant to conventional treatment.

TO THE EDITOR:

I present a case report that illustrates my trial use of an old drug, sulfasalazine (SSZ) in a new way to treat the common but therapeutically difficult clinical problem, chronic rhinosinusitis (CRS), a frequent challenge for the practicing allergist, otorhinolaryngologist, and primary care physician. The patient was a 20-year-old Chinese woman with a history of obstructing nasal polyps and sinusitis for at least 2 years, unresponsive to limited oral and then topical corticosteroids, oral antibiotics, antihistamines, and saline solution sinus rinses while in Hong Kong, China. She underwent sinus surgery in China in 2006, which included nasal polypectomy, with marked improvement in symptoms of nasal obstruction and postnasal drip. Several months later, she moved to the United States and experienced a gradual return of nasal symptoms, including congestion and blockage, which prompted her to seek treatment at the Otolaryngology and Allergy Clinics at the University of Washington Medical Center, Seattle. She denied any history of aspirin or ibuprofen intolerance. *In vitro* allergy testing (ImmunoCap; Phadia, Uppsala, Sweden) to common Northwest inhalant allergens was negative. Results of previous sweat tests performed on 2 separate occasions were negative. Chest radiograph and pulmonary function tests were performed initially and results were found to be normal. Her Rhinitis Control Assessment Test (RCAT) score on several occasions ranged between 12 and 14.¹ (The RCAT, with 6 items, has a score range of 6-30, with scores of 21 or less, indicating rhinitis symptom control problems, with an interest change of 3 points or more representing a significant change in symptoms.) Results of an examination demonstrated thickened, pale nasal mucosa with partially obstructing nasal polyps, most prominent on the left. She was treated with montelukast 20 mg orally per day and intranasal fluticasone 2 sprays each nostril twice daily, without significant symptomatic or examination improvement, RCAT scores remaining in the same range. Computerized tomography (CT) of the paranasal sinuses on November 2012 when compared with a CT of February 2012 demonstrated worsening, with interval transition from near complete to complete opacification of the maxillary sinuses, with a nodular contour of mucosal thickening; and frontal sinuses remained completely opacified, despite her insistence of strict adherence to treatment. The interpreting radiologist was informed of the prior diagnosis but not informed of the specific treatment.

Options for further management presented included an increase in nasal fluticasone or substitution with budesonide

sinus rinse, a limited course of oral prednisone and antibiotics, substitution of zileutin for montelukast, repeated sinus surgery with polypectomy, or a trial of an unproven treatment with nasal SSZ sinus rinse. She chose the SSZ sinus rinse for its ease of use, topical approach, low expense, and historic low risk when used orally for ulcerative colitis (UC). Her instructions were to dissolve a 500 mg SSZ tablet in 120 mL of saline solution in a pediatric sinus rinse bottle the night before the next day's use. This results in degradation of the tablet matrix. Because SSZ is only mildly soluble in water, the patient was instructed to shake the sinus rinse bottle vigorously for 15 seconds before each use, thereby creating a fine particle homogeneous suspension, then administer 2 firm squirts into each nostril so that the rinse would discharge from the contralateral nostril, 3 times daily on a strict regular basis. Treatment was not actually started until late April 2013 because symptoms were becoming progressively worse, with an RCAT score of 09.

When seen in August 2013, after nearly 4 months of topical SSZ sinus rinse monotherapy, she reported moderate improvement, feeling quite well, without significant nasal blockage. Her RCAT scores now ranged between 23 and 25. Physical examination now demonstrated marked reduction in size of the nasal polyps. Repeated CT of paranasal sinuses now demonstrated significant reduction in the bilateral maxillary opacification as well as reduced thickening of the ethmoid air cells, although the frontal sinuses were unchanged (see [Figures E1 and E2](#) in this article's Online Repository at www.jaci-inpractice.org). Each of the completed CT studies obtained showed evidence of prior sinus surgery, including bilateral uncinectomies, an absent anterior portion of middle turbinates, and widening of maxillary sinus ostia.

In an effort to improve medical management in a safe and cost-effective manner, I borrowed from the extensive clinical experience with SSZ, salicyl azo sulfapyridine, and noted its long-time approved use in inflammatory arthritis and bowel disease, particularly UC. UC is characterized by an atypical T-helper cell-2 (T_H2) immune response with high levels of IL-6, IL-10, and IL-13,² somewhat similar to the T_H2 response seen with CRS,³ at least in Western populations. I chose to use SSZ as a sinus rinse based on the known topical colonic anti-inflammatory effect in UC of 1 of its 2 major metabolites, 5-aminosalicylic acid (5-ASA), and SSZ's known stability in suspension for up to 91 days.⁴ After oral administration, colonic bacteria break down SSZ into 5-ASA and sulfapyridine; 5-ASA is poorly absorbed and has an affinity for connective tissue and mucosal surfaces with which it comes into contact, whereas sulfapyridine is largely absorbed. I theorized that, as in the gut, bacteria in the nasopharynx may break down locally administered SSZ into these 2 major components with the resulting 5-ASA exerting a direct topical anti-inflammatory effect on the sinonasal mucosa, which would not be expected to occur with oral administration. Alternatively, in recognizing the reported predominance of a T_H1 response found in nasal polyps of Chinese patients,⁵ although these investigators also describe increased levels of T_H2 cytokines IL-4 and IL-5 in nasal polyps, it may be that the other major metabolite of SSZ, sulfapyridine, which is largely absorbed when given orally and thought to contribute to the benefit seen

in rheumatoid arthritis (RA), a predominantly T_H1 mediated disease, could explain the response in nasal polyps with T_H1 predominant inflammation. Indeed, Michaud and Wolfe⁶ reported fewer sinus problems in patients with RA compared with patients with osteoarthritis and fibromyalgia, especially in those patients with RA who were treated with oral SSZ when compared with patients with RA and those without RA who were not taking this medication. If ultimately shown to be effective, then despite these considerations, the precise mechanism of action remains unknown.

Serious adverse effects of oral SSZ are very rare and may include hematologic effects such as blood dyscrasias, including hemolytic anemia in patients with glucose-6-phosphate dehydrogenase deficiency; azospermia with impaired fertility in men; hypersensitivity reactions, including Stevens-Johnson syndrome, serum sickness, anaphylaxis, and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS); and renal and hepatic toxicity to name a few. Oral use in patients with RA is monitored with a complete blood cell count, chemistry panel with liver function tests and creatinine, and urinalysis at baseline, 1 month, and then every 3 months if there are no abnormalities or other problems identified. Baseline serum glucose-6-phosphate dehydrogenase is obtained in high-risk populations. Although it is highly likely that, when administered as a sinus rinse as opposed to an oral tablet, there will be some absorption through the nasopharyngeal mucosa and some swallowed, the amount absorbed systemically likely would be a fraction of the usual oral dose of 1000 to 1500 mg twice daily for RA.

This case report of a patient with intractable CRS with polyposis who failed many standard medical interventions, with recurrence after surgery, appears to have responded to topical sinus rinse monotherapy with SSZ, although certainly other factors could have contributed to the improvement. Further investigation seems warranted to validate this approach and, if validated, to determine if there is a specific CRS phenotype, genotype, and/or endotype/molecular phenotype that might be especially responsive based on the concepts outlined in the PRACTALL consensus report.⁷ Also, if validated, would it be additive if used in combination with conventional agents?

Ultimately, the determination of efficacy and safety will require the conduct of double-blind placebo-controlled trials and should be guided by recommendations of Meltzer et al.^{8,9} For now, more observational experience from different sources, if favorable, could provide the positive signal to justify that effort.

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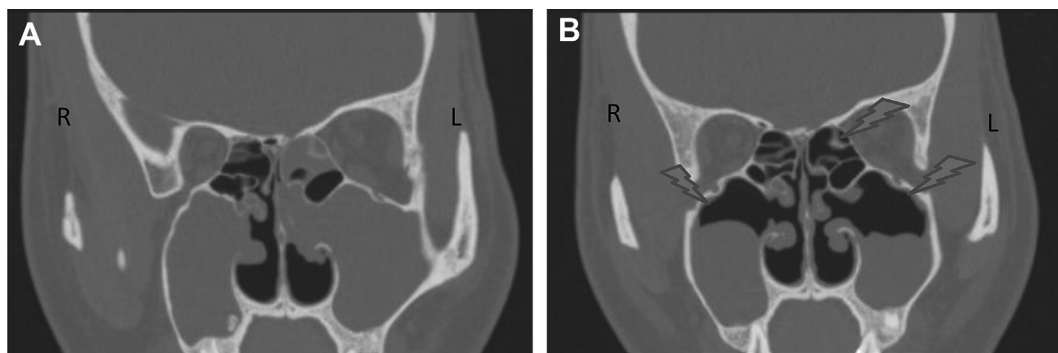


FIGURE E1. CT maxillofacial without contrast. **A**, Before SSZ sinus rinse. **B**, After 4 months, 3 times daily SSZ sinus rinse.

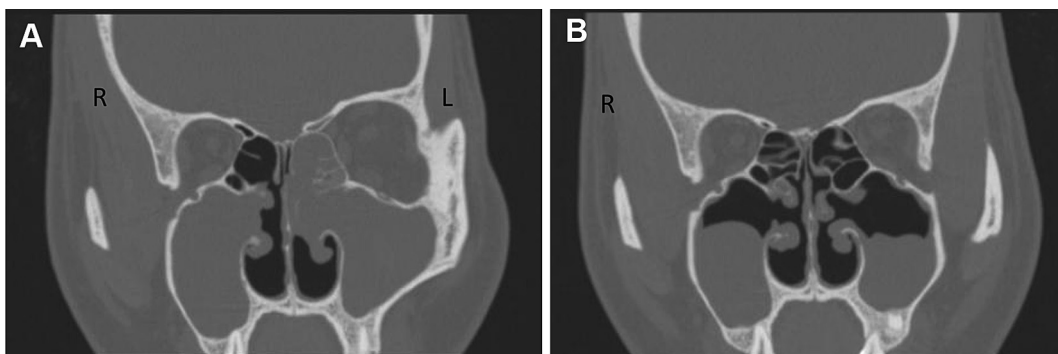


FIGURE E2. CT maxillofacial without contrast. **A**, Before SSZ sinus rinse. **B**, After 4 months, 3 times daily SSZ sinus rinse.

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