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A Multicentered, Open-Label Trial on the Safety and Efficacy of Methylsulfonylmethane in the Treatment of Seasonal Allergic Rhinitis

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ABSTRACT

Background: Seasonal allergic rhinitis (SAR) affects more than 23 million Americans annually, and current epidemiologic studies indicate that its prevalence within the United States is increasing. Numerous clinical observations and case studies have led researchers to hypothesize that methylsulfonylmethane (MSM) may help ameliorate the symptoms associated with SAR.

Objective: The primary goal of this study was to evaluate the efficacy of MSM in the reduction of SAR-associated symptoms. This study also examined possible adverse reactions associated with methylsulfonylmethane supplementation. Finally, this study attempted to elucidate the method of action by which MSM elicits its effect on allergy symptoms.

Design: Fifty-five (55) subjects were recruited for the study. All met the criteria for participation in the study. 50 subjects completed the study. Those subjects completing the study consumed 2600 mg of MSM orally per day for 30 days. Clinical respiratory symptoms and energy levels were evaluated by a Seasonal Allergy Symptom Questionnaire (SASQ) at baseline and on days 7, 14, 21, and 30. Immune and inflammatory reactions were measured by plasma immunoglobulin E (IgE) and C-reactive protein at baseline and on day 30. An additional inflammatory biomarker, plasma histamine, was measured in a subset of subjects ($n = 5$).

Results: Day 7 upper and total respiratory symptoms were reduced significantly from baseline ($p < 0.01$ and $p < 0.005$, respectively). Lower respiratory symptoms were significantly improved from baseline by week 3 ($p < 0.001$). All respiratory improvements were maintained through the 30-day visit. Energy levels increased significantly by day 14 ($p < 0.0001$); this increase continued through day 30. No significant changes were observed in plasma IgE or histamine levels. The results of this study are promising. It would be worthwhile to conduct a larger, randomized, double-blind, placebo-controlled study to establish further if MSM would be a useful agent in the treatment of symptoms associated with SAR.

Conclusion: The results of this study suggest that MSM supplementation of 2600 mg/day for 30 days may be efficacious in the reduction of symptoms associated with SAR. Furthermore, few side effects are associated with the use of this compound. Recent acute and subacute chronic toxicologic data on the same source of MSM as used in this study, further validate the safety of this product.

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INTRODUCTION

Seasonal allergic rhinitis (SAR), a common clinical expression of an atopic reaction to inhaled allergens, affects more than 23 million Americans annually (Centers for Disease Control, 1996). Allergic response varies between individuals and ranges from mild daily symptom recurrences of SAR to debilitating headaches, severe nasal congestion that may lead to sinus infection, and difficulties breathing.

Although current epidemiologic studies indicate that the prevalence of SAR in the United States is increasing (Schoenwetter et al., 2000), conventional treatment for this condition remains palliative. The list of pharmaceutical agents available to chronic allergy sufferers includes a variety of prescription and over-the-counter (OTC) anti-inflammatory mediators. The most common of these agents are H_1-receptor antagonists, which block the activity of histamine. Although these agents are effective in reducing allergy-associated symptoms, the side effects from these antihistamine drugs are troublesome and common (Simons and Sions, 1994). Patients with allergies must often exchange symptoms of allergic rhinitis for such symptoms as sedation, dizziness, tinnitus, fatigue, insomnia, tremors, nausea, epigastric distress, constipation, and diarrhea (Hardman et al., 1996).

Anecdotal observations and clinical case studies indicate that methylsulfonylmethane (MSM) may help to ameliorate SAR-associated symptoms (Cronin, 1999; Jacob and Herschler, 1983; Jacob et al, 1999). This raises the possibility of a specific agent that may aid in the reduction of SAR-associated symptoms without the common troublesome side effects of some pharmaceutical and to a lesser degree, some herbal agents.

MSM is a naturally occurring sulfur compound and a metabolite of dimethyl sulfoxide (DMSO) (Kharasch and Thyragarajan, 1983). Pharmacokinetic studies on the absorption, excretion, and metabolism of DMSO have shown that 17% of orally administered DMSO has been recovered as MSM in urine (Hucker et al., 1967). Both DMSO and MSM have been shown to be incorporated into endogenous cellular matrices (Denko et al., 1967; Kolb et al., 1967; Richmond, 1986); however, whereas DMSO catabolism results in the production of the volatile metabolite dimethyl sulfide (DMS), MSM catabolism does not.

Extensive research has been conducted examining the biologic effects of DMSO (Layman, et al., 1987; Perez-Marrero, 1998; Richmond, 1986). Specifically, DMSO has been shown to elicit an effect on biochemical mediators of inflammation. Animal and *in vitro* studies in humans have shown that DMSO inhibits the synthesis of specific prostaglandins and prostacyclins (Alam and Layman, 1983; Panganamala et al., 1976). Additionally, an *in vitro* study found that DMSO inhibited the proinflammatory cytokines interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α), as well as lipopolysaccharide (LPS)-induced cyclooxygenase 2 (COX-2) expression (Feng et al., 1995).

Although it remains unclear if MSM has the ability to elicit similar biologic responses as DMSO, preliminary studies suggest that MSM may indeed modulate the inflammatory process at some level (Lawrence, 1998; Moore and Morton, 1985). Because DMSO has been shown to inhibit certain biologic mediators of inflammation, MSM may also function in this manner.

The goal of this study was to evaluate the efficacy of MSM in the reduction of SAR-associated symptoms. This study also attempted to explore some plausible methods of action by which MSM might elicit its effect on these symptoms.

METHODS

Recruitment

In order to participate in this study, subjects were required to agree to and sign a written consent form, be between the ages of 21 and 60, and either have been diagnosed with SAR by a qualified health care practitioner or have a history of SAR for 2 or more years, and score above 15 on a preliminary Seasonal Allergy Symptom Questionnaire (SASQ). The study was approved and reviewed by AIBMR Life Sciences, Tacoma, Washington, the Institutional Review Board Human Subjects Review

Committee. Exclusion criteria included pregnant or nursing women and individuals with any serious medical conditions for which they were taking prescription or OTC medication and/or dietary supplements that may influence the outcome of this study. Subjects were recruited via a research pamphlet and notices placed on display at the clinical research sites, local medical family practices in the communities of both clinical sites, and at an alternative and complementary medicine allergy clinic near Tacoma, Washington. Fifty-five (55) individuals were enrolled in this study.

Study design

The study was conducted at two sites, the GENESIS Center for Integrative Medicine (Graham, WA) and the Southwest GENESIS Center for Integrative Medicine (Santa Fe, NM). Thirty-five (35) subjects were enrolled at the GENESIS center (Graham, WA) and 20 subjects were enrolled at the Southwest Center. The months of May and June were chosen in order to ensure high levels of airborne grass and tree allergens. Daily pollen counts were monitored at both sites by values obtained from an online pollen count service (www.pollen.com). Subjects consumed four 650-mg capsules of MSM (Lot Number 8011512; OptiMSM, Cardinal Nutrition, Vancouver, WA) per day for 30 days; two capsules were consumed in the morning and two in the afternoon. A subset of subjects ($n = 16$) that were either nonresponders or who experienced mild response at the initial dose were selected to continue treatment for an additional 14 days. During this time, MSM supplementation was increased to 5200 mg per day, four capsules taken in the morning and four capsules taken in the evening.

Seasonal Allergy Symptom Questionnaire

Clinical allergy symptoms were measured by an SASQ developed by the GENESIS Center for Integrative Medicine. In addition to providing a total score, the SASQ was divided into three subsections measuring upper respiratory symptoms (head, eyes, nose, and throat), lower respiratory symptoms (lungs and chest), and energy level. Subjects were asked to complete the SASQ at baseline and on days 7, 14, 21, and 30. Subjects continuing the study protocol for an additional 14 days were asked to complete an additional SASQ on day 44.

The SASQ was designed by utilizing a list of symptoms that are commonly expressed by individuals suffering from allergic rhinitis. The symptoms listed are the common symptoms associated with immunoglobulin E (IgE) mediated atopic reaction to inhaled allergens that are frequently localized in the upper respiratory tract, nasal mucosa, and conjunctiva. Signs and symptoms such as profuse watery rhinorrhea, paroxymal sneezing, nasal obstruction, and itching of the nose and palate, are included in the questionnaire. Other symptoms, such as sore throat, clearing of the throat, and cough caused by postnasal drainage are also included, as described in *Basic and Clinical Immunology, Eighth edition* (Stites et al., 1994). Because there are often issues with the conjunctiva that can be hyperemic and edematous and that may lead to eyelid swelling from the edema, these symptoms were also included. In addition, atopic patients were requested to list any additional symptoms they suffered from those that were not included in the questionnaire. Symptoms, such as fatigue, lethargy and restlessness, mental confusion, and skin reactions, were added to the original questionnaire in response to patient feedback.

The original design of the questionnaire included both frequency and severity of symptoms, however, after using this instrument in clinical practice for more than 1 year (E.B. and J.R.V.) and obtaining feedback from patients it was redesigned to include only the frequency of symptoms. Many individuals felt that it was difficult for them to subjectively assess the severity of symptoms, such as itching of the nose and palate, sneezing, nasal obstruction, etc. They were, however, able to answer the frequency of the presence of these symptoms accurately.

Subjects who participated in the study were considered to have a clinically significant response to the intervention if they were able to carry out everyday activity without significant discomfort associated with SAR symptoms. Many of the subjects also noted marked im-

Table 1. Mean Differences from Baseline Values for SASQ Scores in SAR Subjects (n = 50; 95% CI)

	Day 7		Day 14		Day 21		Day 30	
	Mean	*CI*	*Mean*	*CI*	*Mean*	*CI*	*Mean*	*CI*
SASQ								
Lower respiratory symptoms	0.31	±0.35	0.37	±0.41	0.67[c]	±0.35	0.47[a]	±0.44
Upper respiratory symptoms	3.53[b]	±2.66	6.80[d]	±2.66	7.90[d]	±3.02	8.50[d]	±2.50
Energy	0.43	±0.60	0.93[d]	±0.43	0.96[c]	±0.47	1.22[d]	±0.48
Total	4.72[a]	±3.36	9.30[d]	±3.31	10.61[d]	±3.68	11.67[d]	±3.45

[a] $p \leq 0.05$.
[b] $p \leq 0.01$.
[c] $p \leq 0.001$.
[d] $p \leq 0.0001$.
SASQ, Seasonal Allergy Symptom Questionnaire; SAR, season allergic rhinitis; CI, confidence interval.

provement in energy levels such that they were able to participate in a full work-day and still have an ability to participate in family and/or sporting activities after work, whereas previously they required caffeine stimulation several times a day just to "get through the work day." This was quite a change for many of these subjects who have a history of using pharmaceutical agents that increase fatigue or attempt to clear up their mental confusion.

Study biomarkers

To elucidate the mechanism of action of MSM, both immune and inflammatory functions were measured at baseline and on day 30 in subjects at both clinic sites. Immune function was measured by plasma IgE and assessed through an inhalant panel measuring 48 different allergens, including grass and weed pollen, fungi, trees, and shrubs (US Biotek Laboratories, Seattle, WA). Inflammation was measured by plasma C-reactive protein (CRP) (US Biotek Laboratories). An additional inflammatory biomarker, plasma histamine, was measured in a subset of subjects, at the Graham, WA site, at baseline and on day 4 ($n = 5$; Nichols Institute Diagnostics, San Juan Capistrano, CA).

STATISTICAL ANALYSIS

Statistical analyses were conducted with the SAS System (SAS Institute, Cary, NC). Individual change in SASQ score was assessed with the paired t test. Univariate analyses and Student's t test for differences in means were conducted on the results of the SASQ and plasma IgE. Nonparametric data analysis was conducted on the histamine data because of the small sample size and likely nonnormality.

RESULTS

Subjects

Fifty (50) subjects (15 males and 35 females; average age 46 years' old) with positive IgE response to inhalants such as grass pollen, weed pollen, fungi, tree and shrub mixes, completed the study; 32 from the Northwest Center and 18 from the Southwest Center. All subjects had a history of SAR for at least the past 2 years with many of them experiencing symptoms for as long as 20 years. Several subjects had undergone several years of allergy desensitization therapy with little improvement of symptoms. Four subjects dropped out of the study during the first week; 3 because of time constraints and 1 because of the development of urticaria after

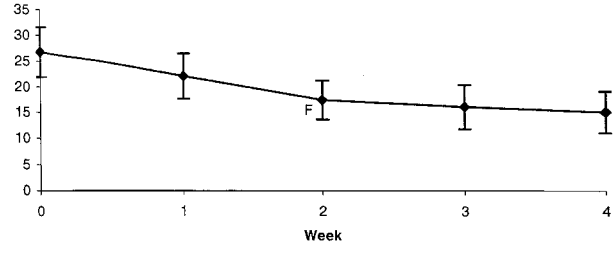

FIG. 1. Total symptoms (mean with 95% confidence interval).

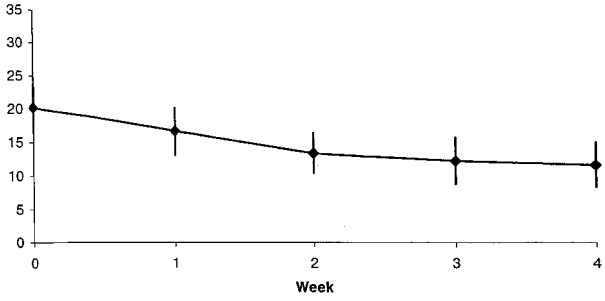

FIG. 2. Upper respiratory symptoms (mean with 95% confidence interval).

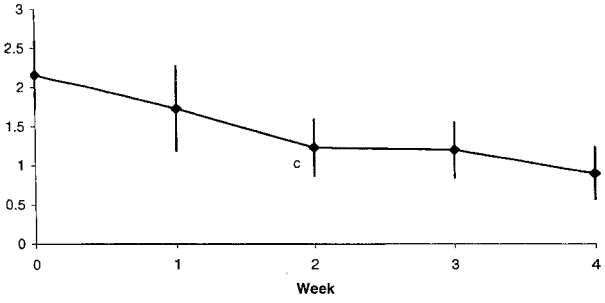

FIG. 4. Energy level symptoms (mean with 95% confidence interval).

the second day of treatment. A fifth subject dropped out during the third week of the study because of the need to consume medications after reporting an increase in allergy symptoms in association with a high pollen count and dry, windy dust-laden weather in the vicinity of the Southwest Center. Endpoint CRP values were not obtained for three subjects because of damage to the vials during transportation to the laboratory.

Outcome measurements

Compared to baseline values (Table 1), upper and total respiratory symptoms were significantly reduced by day 7 ($p < 0.005$ for both; Figs. 1 and 2). Lower respiratory symptoms were improved by week 3 ($p < 0.05$; Fig. 3). These reductions continued through day 30. Energy levels increased significantly by day 14 ($p < 0.05$) and continued to improve through day 30 ($p < 0.0001$; Fig. 4). No significant changes were observed in plasma IgE or histamine levels. Analysis of the CRP data was not performed because of insufficient data on 12 subjects' daily OTC and prescription medication use.

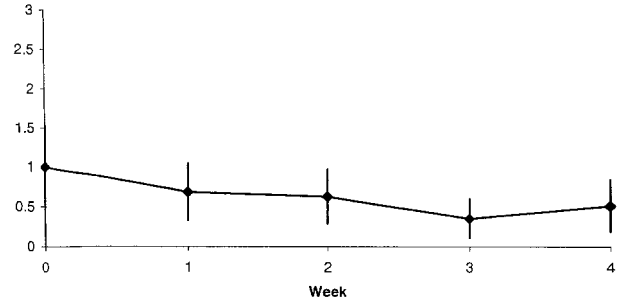

FIG. 3. Lower respiratory symptoms (mean with 95% confidence interval).

In the subset of subjects continuing MSM supplementation for an additional 14 days, energy level and total SASQ scores continued to improve significantly, as compared to baseline ($p < 0.025$ and 0.0001, respectively). However, despite subjects reporting a further reduction in SAR associated symptoms during the 14 days at the higher dosage, no statistically significant changes were seen compared to day 30.

DISCUSSION

To examine the efficacy of MSM in reducing SAR-associated symptoms, 50 subjects suffering from clinical SAR were studied for 30 days. In order to measure subject symptoms uniformly, an allergy questionnaire that would quantify the subjective descriptions by numerical scoring was used. In addition to providing a total score, the SASQ was further divided into three categories (upper respiratory symptoms, lower respiratory symptoms, and energy level); thus, allowing us to obtain more specific information about the nature of the symptoms and any changes occurring throughout the course of the study. Significant improvement was observed in total SASQ scores and in each of the above mentioned SASQ categories with use of MSM over the 30-day trial.

Immune system involvement was assessed by plasma IgE levels at baseline and on day 30. Though no statistically significant changes in plasma IgE levels were found, this does not

rule out an effect of MSM on this immune marker. With conventional desensitization therapies it often takes 12 to 18 months before there is a gradual reduction in plasma IgE levels. Additional studies with larger numbers of subjects over a longer period of time may be warranted to determine the effect of MSM on this marker.

Plasma histamine ($n = 5$) was measures in a subset of subjects at baseline and on day 4. No significant changes were observed for this biomarker; however, lack of statistical power is an obvious factor.

The results of this study are promising but preliminary in nature. These findings lend support to previous clinical observations that MSM supplementation reduces allergy-associated symptoms, and suggest that MSM may be therapeutic in ameliorating some of the symptoms associated with SAR. In addition, we found minimal side effects associated with the use of this product. Further studies examining the effects of MSM on the inflammatory process, including a more extensive evaluation of inflammatory cytokine levels, are necessary to determine the method of action of MSM adequately. A larger, randomized, double-blind, placebo-controlled clinical trial would aid in establishing the use of MSM as a therapeutic agent. Additionally, further human studies examining the method of action of MSM would allow for a detailed description of its physiologic effect.

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