Calcium Glycerophosphate Nasal Spray Reduces Rhinitis Symptoms.

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INTRODUCTION

Intranasal steroids have become the first-line therapy for chronic rhinitis, yet many patients remain symptomatic and/or intolerant of treatment (Jacobs et al., 2009;Tran *et al*., 2011). Even though administered by the intranasal route, steroids, particularly first generation steroids, are adsorbed systemically to some degree [Pien, 2005], and suppression of the hypothalamo-pituitary-adrenal axis has been described in up to 30% of patients using them (Woods *et al*, 2015). Other adverse effects have been described, including perforation of the nasal septum (Cervin and Andersson, 1998), growth suppression in children (Skoner *et al*, 2015; Mener *et al*, 2015; Lee *et al.*, 2014). Recently, we observed that calcium glycerophosphate (CGP), a non-selective phosphatase inhibitor [Tardivel *et al*, 1988], prevented cytokine-induced loss of epithelial integrity in cultured cells [Datta and Weis, 2015]. Furthermore, Baines *et al*. (2014) reported that alkaline phosphatase is elevated in neutrophilic asthma. These two observations lead us to hypothesize that a topical spray of calcium glycerophosphate (CGP), an alkaline phosphatase inhibitor, might preserve epithelial integrity in rhinitis, and consequently be useful in treatment.

METHODS:

The Drexel University Human Research Protection Committee approved this study, listed in clinicaltrials.gov as "Effects of AkPharma's Calcium Glycerophosphate Nasal Spray Wash", NCT01647633.

Sixteen subjects (7 M, 10 F, 38.2 ± 3.49 YOA) were recruited for this study. Of these, three subjects (2 M, 1 F) failed to meet the target composite run-in scores ≥ 5 (0=no symptoms to 3 = severe symptoms) for rhinorrhea, itching, congestion, and sneezing, and three (M) failed to complete the study. The eleven subjects (39.1 ± 4.86 YOA, 2 M, 9 F) completing the study were tested for allergen sensitivities; seven reacted to at least 1 of 26 different allergens, while the remaining four showed no identifiable allergen sensitivities. Two subjects (both F) had a history of asthma, and one subject (M) had been previously diagnosed with COPD.

Treatment consisted of intranasal CGP, formulated as a 3.75% solution in a glycerine/sorbitol/water vehicle.

The solution was administered as a spray (70 µl/spray), delivering approximately 1.5 mg CGP per spray. Subjects were instructed to use 2 sprays per nostril (3.0 mg CGP), twice daily, A.M. and P.M.

Subjects scored AM and PM pre- and post-treatment rhinorrhea, itching, congestion and sneezing for the duration of the study. Results, including pulmonary function tests, were assessed weekly and data analyzed by analysis of variance for repeated measures, followed by Sidak's multiple comparison test, and/or by a post-test for linear trend. All statistical analyses were performed using the Prism 6.0 software package. All values given in this report are mean ± SEM

RESULTS

The cumulative number of sprays per subject, as recorded by the subjects in their daily diary, did not differ between subjects, nor did it differ with time. For the three week duration of the experiment, the mean number of doses per week was 13.8 ± 0.3 (range 18±2 to 9±1).

The morning and evening composite subject scores for rhinorrhea, itching, congestion and sneezing are presented in Figure 1. The mean pre-treatment composite score was 7.34 ± 0.403. Both the pre- and post-treatment scores were significantly ($p<0.0001$) lower than the run-in scores at each time point. Both the AM and PM post-treatment scores were significantly lower than the pre-treatment scores at each time point. When the data were re-analyzed, separating allergic and non-allergic subjects, the results were no different. That is, pre and post-treatment scores were significantly lower than run-in scores at each time point.

Pulmonary function was evaluated at run-in, and on days 7, 14 and 21 of treatment. Because FEV, FEV1, FVC and PEF are dependent on age, gender, height, etc., data were normalized to run-in. Allergic and non-allergic subjects were analyzed separately. Normalized FEV values did not change over the course of the study, and at day 21 were 101.4 ± 3.16% (non-allergic) and 98.5 ± 1.5% of run-in values (N.S.). Similarly, normalized FEV1 values at day 21 were 97.6 ± 2.31% and 98.6 ± 1.52% at run-in (N.S.). On the other hand, FVC increased for the non-allergic group, but not for the allergic group. At day 7, FVC in non-allergic subjects was 107 ± 1.4% of run-in, *vs*. 97.0 ± 1.2 % for allergic subjects ($p<0.001$). By day 21, these values were 113 ± 3.3% for non-allergic subjects *vs*. 99.7 ± 1.5% for allergic subjects ($p<0.001$). Normalized PEF at day 14 was 97.9 ± 5.4% (non-allergic) and 102 ± 3.9% of run-in values (N.S.). At day 21, these values were 85.7 ± 8.3% and 106 ± 3.8% of run in ($p<0.01$).

It is noteworthy that even in this very small study, the WBC declined by about 10% ($p=0.0899$) and the EOS by about 18% ($p=0.104$) over the 21-day course of the study. None of the other blood chemistry parameters were different between day 0 and day 21, nor were they different for allergic *vs.* non-allergic patients.

DISCUSSION

The symptomatic relief is unlikely to be the consequence of a change of seasons, or differing allergen sensitivities. Patients were enrolled in the study over a 14-month period, and exhibited a wide range of sensitivities, yet the decline in diary scores remained remarkably consistent between subjects. Furthermore, a sister study conducted in New Mexico (data not presented here) produced much the same results, despite being performed at a different time, by different investigators, and in a part of the country having a very different ambient allergen profile as compared to Philadelphia.

The small increase in FVC in non-allergic subjects is intriguing and bears further investigation. While the average increase in FVC was small, it suggests that treatment may improve pulmonary compliance. The decrease in PEF at day 21 is most likely attributable to a single subject, whose day 21 PEF was 62% of run-in, while the day 7 and 14 PEF values for this patient were 97.5 and 97.9%, respectively, of run-in. It is important to note that this was a 21 day study, and neither the diary-score nor the FVC data have reached plateau. It seems reasonable to speculate that both parameters may continue to improve. Similarly, the decreases in WBC and EOS were remarkable for a short study of only 11 patients.

These data demonstrate that intranasal CGP effectively reduces the symptoms of rhinitis. Both the pre-treatment and post treatment symptom scores decreased markedly over the course of the study. The objective data, an increase in FEV and decreases in WBC and EOS, are consistent with the declining symptom scores. Together, the objective and subjective data suggest that the effect of intranasal CGP is not the consequence of washing irritants away from the nasal passages, but results from a longer-lasting pharmacologic effect.

Calcium glycerophosphate is classified as “generally recognized as safe” by the FDA. As glycerophosphate is a normal metabolic intermediate, it is unlikely to have significant abuse liability, even when used over a long period of time. Twice daily use as a nasal spray not only provided symptomatic relief, but also may have a mild effect on pulmonary function. These properties make calcium glycerophosphate an attractive candidate for rhinitis treatment.

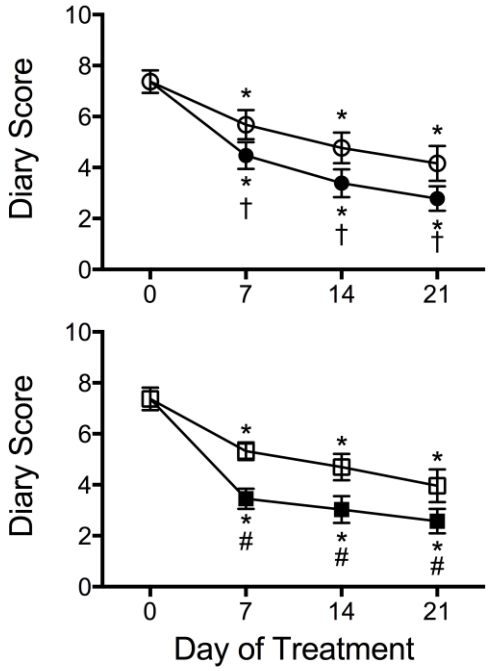

Figure 1. Mean pre- and post-treatment diary scores for symptoms. Both pre-and post-treatment scores were significantly ($p < 0.0001$) lower than the run-in (day 0) score for each of the treatment days. The pre- and post-treatment scores were significantly different for each time point for both A.M. and P.M. Open symbols = Pre-treatment, closed symbols = Post-treatment. *=$p<0.0001$ *vs.* day 0; †=$p<0.05$ *vs*. day 0; #=$p<0.0001$ *vs*. day 0 as determined by ANOVA for repeated measures followed by Sidak's multiple comparison test.

Cervin A1, Andersson M. Intranasal steroids and septum perforation--an overlooked complication? A description of the course of events and a discussion of the causes. Rhinology. 1998 Sep;36(3):128-32.

Datta P, Weis MT. Calcium glycerophosphate preserves transepithelial integrity in the Caco-2 model of intestinal transport. World J Gastroenterol. 2015 Aug 14;21(30):9055-66. doi: 10.3748/wjg.v21.i30.9055.

https://www.clevelandclinicmeded.com/medicalpubs/ccjm/december2005/pien.htm - systemic absorption of intranasal steroids

Jacobs R, Lieberman P, Kent E, Silvey M, Locantore N, Philpot EE. Weather/temperature-sensitive vasomotor rhinitis may be refractory to intranasal corticosteroid treatment. Allergy Asthma Proc. 2009 Mar-Apr;30(2):120-7. doi: 10.2500/aap.2009.30.3206.

Lee LA, Sterling R, Máspero J, Clements D, Ellsworth A, Pedersen S. Growth velocity reduced with once-daily fluticasone furoate nasal spray in prepubescent children with perennial allergic rhinitis. J Allergy Clin Immunol Pract. 2014 Jul-Aug;2(4):421-7. doi: 10.1016/j.jaip.2014.04.008. Epub 2014 May 21.

Mener DJ, Shargorodsky J, Varadhan R, Lin SY. Topical intranasal corticosteroids and growth velocity in children: a meta-analysis. Int Forum Allergy Rhinol. 2015 Feb;5(2):95-103. doi: 10.1002/alr.21430. Epub 2014 Nov 3.

Nguyen P Tran, John Vickery, and Michael S Blaiss Management of Rhinitis: Allergic and Non-Allergic Allergy Asthma Immunol Res. 2011 Jul; 3(3): 148–156.

Skoner DP, Berger WE, Gawchik SM, Akbary A, Qiu C. Intranasal triamcinolone and growth velocity. Pediatrics. 2015 Feb;135(2):e348-56. doi: 10.1542/peds.2014-1641.

Tardivel S, Razanamaniraka L, Porembska Z, Crouzoulon G,Fournier P, Dupuis Y. Homodimer and heterodimer forms of adultrat intestinal alkaline phosphatase. Life Sci 1988; 43: 2059-2065

Woods CP, Argese N, Chapman M, Boot C, Webster R, Dabhi V, Grossman AB, Toogood AA, Arlt W, Stewart PM, Crowley RK, Tomlinson JW. Adrenal suppression in patients taking inhaled glucocorticoids is highly prevalent and management can be guided by morning cortisol. Eur J Endocrinol. 2015 Nov;173(5):633-42. doi: 10.1530/EJE-15-0608. Epub 2015 Aug 20.