Calcium Glycerophosphate Nasal Spray Reduces Rhinitis Symptoms.

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ABSTRACT

Rationale: Many patients with rhinitis remain symptomatic and/or intolerant of treatment. Recently, Baines *et al.* (2014) reported that ALP is elevated in neutrophilic asthma, leading us to hypothesize that a topical spray of calcium glycerophosphate (CGP), an ALP inhibitor, might be useful in treating rhinitis.

Methods: This study was approved by the Drexel University Human Research Protection Committee. Twelve subjects (37±4.7 YOA, 3M, 9 F) with target composite run-in scores ≥ 5 (0=no symptoms to 3=severe symptoms) for rhinorrhea, itching, congestion, and sneezing were treated with intranasal CGP (30 mg/nostril, b.i.d., as a spray) over 3 weeks. Subjects scored AM and PM pre and post treatment rhinorrhea, itching, congestion and sneezing for the three-week period of the study. Results, including pulmonary function tests, were assessed weekly and data analyzed by analysis of variance for repeated measures.

Results: The mean pre-treatment composite score was 7.24±0.465. The score declined significantly (p<0.0001) over the period of the study, to 3.88±0.684 (AM, pre), 2.53±0.453 (AM, post), 3.94±0.636 (PM, pre) and 2.57±0.480 (PM, post). There was a linear trend to increase FVC (p=0.0112), but not FEV1 or PEF. The mean WBC tended to decline over the course of the study from 7.38±0.58 x 10^3 to 6.67±0.52 x 10^3 (p=0.0899). Similarly, EOS tended to decline from 2.52±0.77% at run-in to 2.08±0.48% (p=0.104)

Conclusions: These data demonstrate that intranasal CGP effectively reduces the symptoms of rhinitis. More importantly, even in this very small study, treatment showed a trend to improve FVC. Both WBCs and EOS trended down from the upper to the mid range of normal, suggesting that treatment reduced the general state of inflammation. The CGP molecule is classified as "generally recognized as safe" by the FDA. As a normal metabolic intermediate, it is unlikely to have significant abuse liability, even when used over a long period of time. These properties make it an attractive candidate for rhinitis treatment.

INTRODUCTION

Many patients with rhinitis remain symptomatic and/or intolerant of treatment. Recently, Baines *et al.* (2014) reported that alkaline phosphatase is elevated in neutrophilic asthma, leading us to hypothesize that a topical spray of calcium glycerophosphate (CGP), an alkaline phosphatase inhibitor, might be useful in treating rhinitis.

METHODS

The Drexel University Human Research Protection Committee approved this study. 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 two (M) failed to complete the study. Twelve subjects (38.2 ± 3.49 YOA, 3 M, 9 F) completed the study. Subjects were tested for allergen sensitivities; of the twelve subjects completing the study, eight subjects reacted to from 1 to 26 different allergens, while the remaining four subjects 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 (30 mg per nostril, b.i.d., as a spray) over 3 weeks. Subjects scored AM and PM pre- and post-treatment rhinorrhea, itching, congestion and sneezing for the three-week period 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, 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 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.

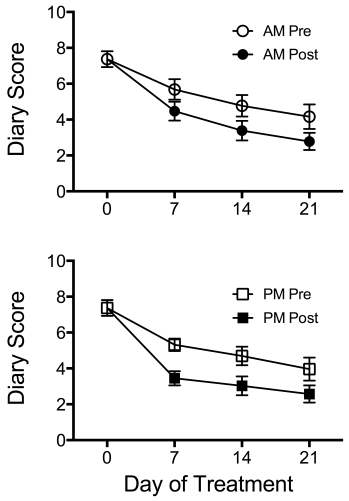
The cumulative number of sprays per subject, as recorded by the subjects in their daily diary, is shown in Table 1. Two-way analysis of variance showed that dosing did not differ between subjects, nor did it differ with time.

Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC) and peak expiratory flow (PEF) were used to evaluate pulmonary function at run-in, and on days 7, 14 and 21 of treatment. FEV1 did not change over the course of the study, and was 2.88 ± 0.27 liters at run-in and 2.85 ± 0.26 liters at day 21. Similarly, PEF was 6.15 ± 0.53 L/sec at run-in and 6.04 ± 0.56 L/sec at day 21. On the other hand, as shown in Figure 2, FVC increased significantly, by about 166 ± 92 mL, over the course of the

Results, con't

study. Interestingly, the greatest increase in FVC (0.59L, 17%) was in the one patient previously diagnosed with COPD. FEV1/FVC decreased slightly but significantly, as a consequence of the increase in FVC.

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 (see Table 2). None of the other blood chemistry parameters were different between day 0 and day 21.



Sidak's multiple comparisons test, Difference Between Pre and Post

	Mean Diff.	95% CI of diff.	Significant?
AM			
Run-in	0	-1.13 to 1.13	NS
Day 7	1.209	0.080 to 2.34	p < 0.05
Day 14	1.385	0.256 to 2.52	p < 0.05
Day 21	1.382	0.252 to 2.51	p < 0.05
PM			
Run-in	0	-0.761 to 0.761	NS
Day 7	1.868	1.11 to 2.63	p < 0.0005
Day 14	1.664	0.903 to 2.42	p < 0.0005
Day 21	1.391	0.630 to 2.15	p < 0.0005

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 score for each of the treatment days. The pre- and post-treatment scores were significantly different for each time point for both A.M. (p < 0.05) and P.M (p < 0.01), as determined by analysis of variance for repeated measures followed by Sidak's multiple comparison test.

Day	Cumulative Sprays (Mean ± SEM)
7	14.1 ± 1.08
14	14.4 0.77
21	13.7 ± 0.94

Table 1. Subjects recorded the number of sprays per day in their diary. The cumulative number of sprays per week did not differ during the course of the study

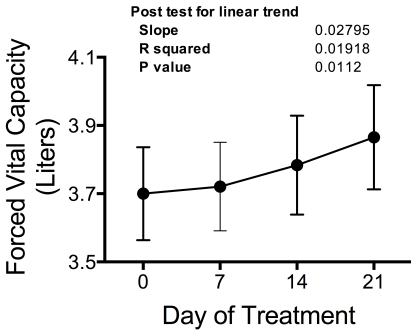


Figure 2. There was a small but statistically significant linear trend to increase FVC over the time course of the study. Slope = 0.0280, p =0.0112

	Run-In	Day 21		Run-In	Day 21
WBC	7.38 ± 0.58	6.67 ± 0.52	EOS	2.52 ± 0.77	2.08 ± 0.48
RBC	4.60 ±0.08	4.54 ±0.08	Chloride	101 ± 0.69	101 ± 0.64
Hbg	13.4 ± 0.32	13.2 ± 0.36	Bicarbonate	24.9 ± 0.73	25.3 ± 0.69
Hct	40.2 ± 0.95	39.6 ± 0.84	BUN	12.6 ± 1.65	13.9 ± 1.45
PLT	263 ± 26.1	258 ± 25.3	Calcium	9.45 ± 0.11	9.52 ± 0.11
Total Protein	7.19 ± 0.19	6.95 ± 0.14	Total Bilirubin	0.425 ± 0.07	0.433 ± 0.07
Albumin	4.42 ± 0.14	4.33 ± 0.12	Alk Phos	66.7 ±6.2	63.4 ± 6.8
Glucose	97.1 ± 6.35	87.6 ± 6.23	AST	24.1 ± 4.8	25.4 ± 7.1
Sodium	139 ± 0.74	138 ± 0.45	Phosphorus	3.5 ± 0.12	3.66 ± 0.14
Potassium	4.08 ± 0.07	4.06 ± 0.09	ALT	19.2 ± 4.4	18.7 ± 5.1

Table 2. White blood counts and eosinophils tended to decline, while blood chemistry values did not differ, between run-in and day 21.

DISCUSSION

- **Symptomatic relief was unlikely 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 subjective and objective data demonstrate that intranasal CGP effectively reduces the symptoms of rhinitis.**
  Subjectively, both the pre-treatment and post treatment symptom scores decreased markedly over the course of the study. Objectively, an increase in FEV and decreases in WBC and EOS, are consistent with the declining symptom scores.
- **The small increase in FVC is intriguing and bears further investigation.**
  While the average increase in FVC was small, it suggests that treatment may improve pulmonary compliance. It is important to note that this was a 21 day study, and neither the diary-score nor the FEV 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 12 patients.
- **Calcium glycerophosphate is an attractive candidate for rhinitis treatment.**
  It is classified as "generally recognized as safe" by the FDA. As glycerophosphate is a normal metabolic intermediate, CGP 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.

REFERENCES

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