Efficacy of intranasal fluticasone propionate nano nasal spray in management of chronic rhinitis: a randomized clinical trial

Yasir Mehmood,[1,2] Hira Shahid[2,3]

[1]Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Government College University Faisalabad, Faisalabad, Pakistan; [2]Saffron Pharmaceuticals Pvt Ltd., Faisalabad, Pakistan; [3]Department of Pharmacology, Faculty of Pharmaceutical Sciences, GC University Faisalabad, Faisalabad, Pakistan

ABSTRACT

Common inflammatory conditions of the airways, such as chronic rhinitis, nasal polyposis, seasonal and chronic allergic rhinitis can greatly affect a patient's health and quality of life. For each of these disorders, intranasal corticosteroids are suggested as a component of the therapy regimen because they can assist to lessen symptoms by reducing inflammation. In this randomized controlled trial, 30 people with rhinitis were enrolled to evaluate a new nano formulation of fluticasone propionate nano-nasal spray (FP-NNS) with commercially available nasal spray called FP-NS for the treatment of allergic rhinitis (15 to 60 years). 50 mcg dosages of FP-NNS were administered to patients in the morning and evening. This regimen was administered as a nasal spray for a 4-week effectiveness and safety phase. Analysis of variance was used to evaluate each efficacy endpoint. More of our clinical studies have shown that FP-NNS reduces inflammatory indicators in adults and children.

Introduction

Chronic rhinitis (CR), a frequent inflammatory condition of the sinuses and nasal passages, can greatly reduce a person's ability to go about their everyday lives and their quality of life.[1] Nasal congestion and a runny nose that lasts for at least 12 weeks are typical symptoms.[2] However, topical and systemic steroid usage is essential to the management of this illness. Treatment strategies for patients with CR entail a complex combination of surgical and pharmaceutical therapies.[3] In order to treat CR, which is resistant to standard medical therapy, endoscopic sinus surgery (ESS) clears the sinuses, improves sinus airway patency, and lessens the intensity of inflammation. It is well known that this is the preferred surgical technique.[4] However, although not always a simple and benign procedure, possible complications include poor surgical results, extensive postoperative bleeding, mucosal adhesions, infection, and inflammation. On the other hand, because of their powerful anti-inflammatory characteristics, steroids are frequently utilized in the treatment of CR.[5]

Ig-E-mediated immune response was triggered when the human nasal mucosa was exposed to natural allergens, and this could result in a chronic inflammatory disease like chronic rhinitis (CR). The symptoms of CR may be seasonal or persistent.[6] Allergens such animal saliva and dander from cockroaches, dust mites, and mold can cause intermittent or continuing symptoms in patients with chronic CR. Rhinorrhea, postnasal drip, nasal discomfort, nasal congestion, and sneezing are all symptoms of CR. Other symptoms that patients experience include non-nasal, such red, itchy, or watery eyes.[7] Nasal congestion is one of the most prevalent and frequently the most bothersome symptoms. It is associated with sleep problems, which can harm cognitive function, lower health-related quality of life, and create psychosocial dysfunction.[8]

Correspondence: Yasir Mehmood, Department of Pharmaceutics, Faculty of Pharmaceutical Sciences, Government College University Faisalabad, Faisalabad, Pakistan.
E-mail: Yasir_dpharm@hotmail.com

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The primary objectives of CR treatment are to avoid or reduce symptoms as safely and effectively as feasible.[9] Intranasal corticosteroids are viewed as the first-line treatment for chronic CR in addition to effective prevention strategies since they lessen both the early and late stages of the immune response.[10] These drugs reduce the amount of pro-inflammatory cells and release of cytokines, as well as the mediators released by mast cells and basophils that are mediated by Ig-E. Additionally, their ability to reduce mucous membrane permeability and nasal discharges aids in the relief of CR symptoms.[11]

Fluticasone propionate (FP) has been demonstrated to be effective in treating nasal inflammatory disorders.[12] It has been used in clinical practice for sinus indications for over 20 years, and extensive literature demonstrates beneficial properties for such conditions.[13] FP is a highly lipophilic, sparingly water-soluble (0.0108 mg/mL) drug with relatively low risk of systemic absorption.[14] Bioavailability is reported to be less than 11%, but a study of repeated doses of inhaled corticosteroids suggests a bioavailability of 11%.[14] Poor water solubility of drugs is one of the biggest problems in drug development.[15]

The objective of this research is to prepared nano nasal spray loaded with FP (FP-NNS) shown in Figure 1 and evaluate the efficacy and safety of FP-NNS 50-µg doses/actuator administered once daily in the morning in the treatment of patients with CR. FP-NNS was new prepared nano nasal spray by using polymers silica[16] which was chemically tested and approved by all means and found within specifications of USP 42 (Figures 2 and 3).

Trial design

This randomized fixed-dose clinical research was conducted across many centers in Punjab Pakistan. The research was planned to compare the therapeutic efficacy of commercial nasal spray (FP-NS) and nano nasal spray (FP-NNS). This experiment included a 4-week effectiveness and safety phase. The major efficacy metric for the time period was the mean change in the total nasal symptom score (TNSS) as assessed by a physician from baseline to day 28. An allergen-specific immunoglobulin E (IgE) test was performed within three time points (in start, after 14 days and 28th day). Other important lab tests were also performed by 1st day, 14th day and 28th day to determine toxic effect of nano particles. Individual nasal symptoms, total symptom score, and subject evaluated TNSS are among the additional efficacy measures in the phase (TSS, non-nasal and nasal symptoms, summed). The study was place between July and August of 2022; the first participant signed up on July 4th and the last subject was visited to finished on August 22, respectively. The study therefore started after the height of the German grass pollen season (which is around May or June). During the study side effect were also determined for at least 8 weeks after starting treatment.

Ethical standard

The Rashid Latif Medical and Pharmacy College and Hospital in Lahore, Pakistan, has an ethical committee that has given its approval for this study, which was carried out in compliance with the Helsinki Declaration (RLCP-ID: CT-RLCP-000134-2022).

Efficacy evaluations

Based on their severe nasal rhinitis symptoms over the past 12 hours, patients were evaluated throughout

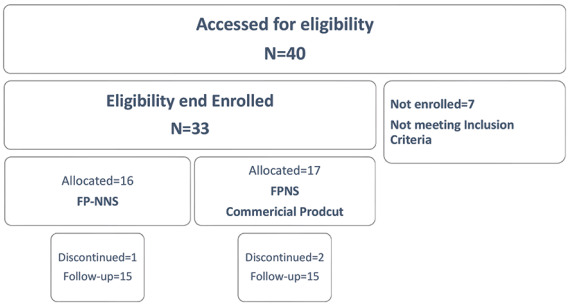

Figure 2. Flow chart of the subjects throughout the study.

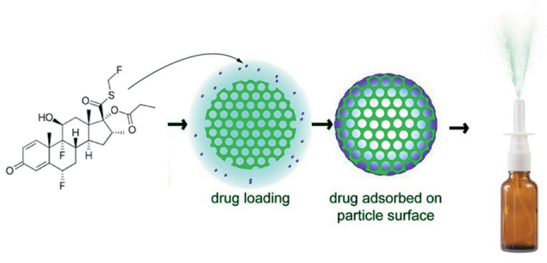

Figure 1. Schematic diagram of preparation of fluticasone propionate-nano nasal spray.

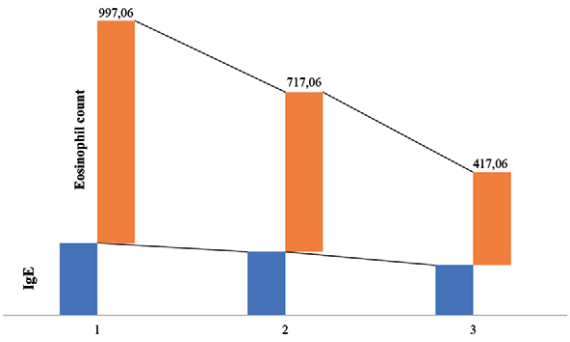

Figure 3. Mean change from baseline to 14th days and 28th day. IgE, immunoglobulin E.

therapy. Every patient received a paper form/file from the doctor that was used to record their symptoms twice a day: when they first started in the morning before medication and roughly 12 hours later in the evening. Every patient was visited to doctor after 14 and 28±days for IgE test which was performed in nearest pathology lab. Observations or symptoms were made, and they were recorded in the patient's file by the patients. The investigator remained connect with patients and study center's administration (doctors' clinic). The doctor assessed the severity of the symptoms at the baseline (day 1), 14 day and 28 visits.

Safety evaluation

At the beginning of clinical trial, a doctor or investigator evaluated the patient condition. The subject's general health status was also observed up until the final visit based on the examination. Investigator was directly connected with patients to follow-up the adverse events (ADE) and coming visit to the doctor. All ADR were documented by investigator and patients were also advised to write-down all ADE.

Criteria

Inclusion criteria

1. Patients both male and female older than 12 years old.
2. Who can be able to understand and fill the consent form and file or guardian of children who is willing.
3. Who has congestion issue on visit to doctor.
4. No history of drug hypersensitivity.
5. At least a 2-year history of CR.
6. Good Health in general and absence of any condition or concurrent therapy that might affect the study's results.

Exclusion criteria

1. Known current pregnancy.
2. Current hospitalization.
3. Within the last 12 months, had sinus surgery or nasal surgery.
4. More than three episodes of chronic sinusitis each year.
5. Travel arrangements made outside the study region throughout the research period.
6. Unable to complete online questionnaires or adhere to study requirements.
7. Kidney failure or dialysis; severe liver disease or cirrhosis.
8. History of SARS-CoV-2 infection.
9. Infections of the respiratory tract within last 30 days.

Statistical analysis

EXCEL software was used for data administration and for databases entries. For statistical analysis, SPSS 25.0 was employed. A proposed inquiry has a 95% confidence interval between prepared nano nasal spray FP-NNS and commercial nasal spray FPNS. In this study, one-way analysis of variance (ANOVA) was also employed to compare the symptoms between the two groups.

Results

The trial includes 30 participants (15-60 years old) who receive FPNS commercial product and FP-NNS 50 mcg/dose. Clinical and demographic traits were comparable between the two groups. All subjects had completed the trial and they were actively participated and answer all the questions asked by doctors and investigators. In comparison to participants who were treated with FP-NNS had significantly lower levels of symptoms regarding TNSS from baseline to day 14 and 28. Similar results with notable improvements were found for FP-NNS regarding IgE level. At baseline, subjects who had received FP-NNS treatment had significantly better overall rhinitis conditions as well than those who had received FPNS commercial product. Throughout the period, both groups showed a general trend toward ongoing improvement in the overall status of rhinitis as determined by a physician.

Baseline clinical characteristics

According to the inclusion criteria, 30 patients were enrolled in the study and randomly divided into 2 groups. Randomly assigning 15 patients to receive intranasal FPNS as group I and 15 patients to receive intranasal FP-NNS as group II and these participants had 28 days follow-up. 30 patients' demographics and baseline characteristics were recorded assessed for primary parameters across 28 days period and clinical patient features were comparable across groups. The first group included 8 male (53%) and 7 female (47%) patients, and the second group included 6 male (40%) and 9 female (60%) patients, with a mean age of 39.1 and 34.6 years. The baseline means and standard deviation (SD) of the demographic factors did not differ statistically significantly from one other (Tables 1 and 2).

Clinical efficacy

Fifteen patients in group II and a total of 15 patients in group I was evaluable and took part in the efficacy analysis. Visual analogue total nasal symptom scores (VATNSS), visual analogue total ocular symptom scores (VATOSS), IgE level and absolute eosinophil counts were considered for the efficacy analysis. Clinical improvement was seen in all groups across all primary measures, which demonstrated a statistically significant decrease in symptom severity over the course of 28 days. Group I, on the other hand,

demonstrated statistically more improved disease progression as well as a decline in symptom severity, IgE level and eosinophil count shown in Table 3.

Safety

The number of adverse events (AEs) was similar between the FPNS and FP-NNS groups, and most AEs were rated as mild to moderate and unrelated to therapy at both times. For MFNS and MF-NNS, respectively, fatigue (6.6 and 6.6%), nausea (0 and 6.6), headache (46.6 and 13.3%), insomnia (13.3 and 26.6), pruritus (13.2 and 6.6%), coughing (40 and 13%) and arthralgia (6.6 and 13.33%) were the most frequently reported treatment-related adverse events (AEs) over the time. Apparently all these AEs were drug related and no one special AEs was seen throughout the study.

Discussion

Perennial CR can begin early in life and could be an indication of allergies or other respiratory issues in the future. Intranasal corticosteroids are delivered directly to the nasal mucosa, where these can reduce anti-inflammatory actions, diminish nasal itching, sneezing, rhinorrhea, and nasal congestion. Intranasal corticosteroids can successful treatment the CR. According to the findings of the current investigation, MF-NNS was considerably more successful than FPNS commercial product at reducing rhinitis symptoms in patients aged 15 to 60. Because FP-NNS are nano particles which can enhance drug absorption and bioavailability. FP was loaded into mesoporous silica nanoparticles (MSN) and due to its unique properties, including biocompatibility, biodegradability, and non-toxicity these are widely

Table 1. Baseline characteristic of both groups.

Characteristics	Group 1 FP-NNS (n=15)	Group 2 FPNS (n=15)
Age	39.1±14.0	34.6±12.9
Male	8(53%)	6(40%)
Female	7(47%)	9(60%)
IgE IU/mL	323.91	392±71.42
Eosinophil count cells/mcL	997.06±142.14	934.37±254.72
VATNSS		
1. Nasal congestion	7.28±1.23	8.90±1.13
2. Rhinorrhea	8.22±1.51	7.62±1.72
3. Sneezing	9.86±0.71	9.47±0.39
4. Nasal Itching	9.69±1.24	9.08±1.41
VATOSS		
1. Watery eyes	5.59±1.52	6.20±1.43
3. Redness	8.78±1.53	7.97±1.65
4. Burning	7.90±1.30	7.60±1.29
5. Itching eyes	7.73±1.42	8.65±1.30

FP-NNS, fluticasone propionate-nano nasal spray; FPNS, fluticasone propionate nasal spray; VATNSS, visual analogue total nasal symptom scores; VATOSS, visual analogue total nasal symptom scores.

Table 2. Adverse events reported during the study period 28 days.

	Adverse events			
	FP-NSS (15)	%	FPNS (15)	%
Fatigue	1	6.6	1	6.6
Nausea	1	6.6	0	0
Headache	2	13.3	7	46.6
Insomnia	4	26.6	2	13.3
Pruritus	1	6.6	2	13.2
Anemia	0	0	0	0
Cough	2	13.3	6	40
Arthralgia	2	13.3	1	6.6

FP-NNS, fluticasone propionate-nano nasal spray; FPNS, fluticasone propionate nasal spray.

used for drug administration.[17] Size of our MSN was about 400 nm which can ready absorb within nasal cavity to deliver the drug.[18,19] These results were supported by study of particular nasal symptoms: scores with FP-NNS significantly dropped more than with FPNS throughout the duration of days 1-28. Both doctors and investigators reported that FP-NNS therapy reduced both the overall severity of rhinitis and the response to therapy.

The findings of this investigation support a dose-range trial in seasonal CR patients aged 15 to 60 years, where FP-NNS intake at 50 mcg/day was significantly more beneficial than FPNS commercial product at lowering the physician's estimated rate. It was mentioned that doctors have claimed that FP-NNS has led to a higher improvement in symptoms. There were no fatalities or serious adverse events reported. There were no serious negative occurrences recorded in the subjects. No treatment group showed any clinically significant changes in laboratory data, vital signs, or limited physical tests. 30 participants in all completed the trials.

Table 3. Characteristics.

Parameters	**Characteristics, n=30**		
Age	15-60		
Male, n (%)	14 (46.66%)		
Female, n (%)	16 (53.33%)		
Diabetes, n (%)	4 (13%)		
Hypertension, n (%)	5 (16.6%)		
Median laboratory values 1st day			
	FP-NNS (15)	**FPNS (15)**	**P value**
ALT, U/I	Between 12-30	Between 15-30	0.32
AST, U/I	Between 21-38	Between 21-28	0.15
ALP, IU/I	Between 40-90	Between 45-90	0.14
CRP, mg/L	Between 8-10	Between 8-10	0.13
LDH, U/L	Between 140-198	Between 149-200	0.23
IgE (kUA/L)	323.91	392±71.42	0.31
Eosinophil count cells/mcL	917.06±249.14	904.37±244.79	0.21
Median laboratory values after 14 days treatment			
	FP-NNS (15)	**FPNS (15)**	**P value**
ALT, U/I	Between 13-27	Between 16-29	0.23
AST, U/I	Between 19-32	Between 21-38	0.36
ALP, IU/I	Between 53-78	Between 63-89	0.23
CRP, mg/L	Between 6-10	Between 7-11	0.25
LDH, U/L	Between 127-188	Between 187-201	0.33
IgE (kUA/L)	283.91	291±71.42	0.32
Eosinophil count cells/mcL	717.06±249.14	604.37±244.79	0.23
Median laboratory values after 28 days treatment			
	FP-NNS (15)	**FPNS (15)**	**P value**
ALT, U/I	Between 8-31	Between 12-28	0.32
AST, U/I	Between 9-28	Between 24-31	0.42
ALP, IU/I	Between 33-78	Between 43-90	0.23
CRP, mg/L	Between 7-10	Between 7-9	0.15
LDH, U/L	Between 117-210	Between 127-189	0.13
IgE (kUA/L)	223.91	192±71.42	0.22
Eosinophil count cells/mcL	417.06±249.14	304.27±244.79	0.31

FP-NNS, fluticasone propionate-nano nasal spray; FPNS, fluticasone propionate nasal spray; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; CRP, C-reactive protein; LDH, lactate dehydrogenase; IgE, immunoglobulin E.

Conclusions

At the conclusion of the experiment, FP-NNS doses of 50 mcg administered once day considerably reduced the severity of rhinitis, with differences reaching statistical significance with commercial drugs. After 28 days of testing with both Fluticasone Propionate nasal spray and FP-NNS, FP-NNS showed statistically higher decreases in congestion than the control group. This study shows that FP-NNS 50 mcg has favorable efficacy and safety profiles in Pakistani populations (15-60 years), suggesting its usage in therapeutic treatment for CR. FP-NNS is an effective and well-tolerated treatment for seasonal rhinitis in both adults and children. It reduces the nasal symptoms of nasal obstruction and congestion.

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