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SIDE EFFECTS AMONG DUONASE (FLUTICASONE WITH AZELASTINE COMBINATION) NASAL SPRAY USERS

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ABSTRACT

Introduction: Vasomotor Rhinitis and Allergic Rhinitis are the common indications for intranasal therapy of Azelastine along with Fluticasone (DUONASE). Regular follow-up is required during this therapy to observe any side effects like cognition impairment, ear infections, etc. **Aims:** Safety profile evaluation on Rhinitis patients with the use of DUONASE NS (Nasal Spray) **Materials and Methods:** We carried out a prospective observational study on DUONASE users. DUONASE users were selected at ENT OPD after obtaining their prior consent. In our study, we screened 140 DUONASE users in various age groups. **Statistical analysis used:** We analyzed the data obtained from the study by using Microsoft Office Excel 2019. **Results:** Out of 140 DUONASE users screened, the number of users without side effects was 100 (71.43%) while the users with side effects were 41 (29.2%). Of the 41 users with side effects, 20 were having headaches, 11 were having coughs, and 09 were found to have dysgeusia. In the entire study, 44 users have a previous history of hyperacidity. None of the users had somnolence. **Conclusions:** Most of duonase users have headaches and coughs as side effects. This indicates that the users with headache and cough should be reassured of safety and the users with epistaxis should be followed up frequently and should be educated regarding nasal hygiene.

KEYWORDS : dysgeusia, DUONASE, cough.

INTRODUCTION

Fluticasone, a steroid preparation used as a nasal spray. A compound that can't be used as an acute treatment in any condition but can be used as a maintenance treatment or prophylaxis therapy in conditions like asthma and nasal symptoms of rhinitis. The formulations and strengths available in each actuation in each spray or each breath are 44mcg, 110mcg and 220mcg. (1) The warnings issued by WHO & FDA for fluticasone are anaphylaxis and osteoporosis on their issue of 2011 of this particular drug. Other known side effects/warnings of fluticasone are immunosuppression, Candida Albicans, HPA axis suppression, growth retardation in the pediatric population, and glaucoma & cataract. (2) According to clinical trial data, there was no difference in ADR incidence and ADR types in short-term usage of 12-16 weeks or long-term usage of 27 - 56 weeks. But regularly expected ADRs are nausea, vomiting, arthralgia, articular rheumatism, malaise, and fever. In post-marketing surveillance new ADRs are reported, they are Aphonia, behavioral changes in children like agitation, anxiety, irritation in children, and Churg-Strauss Syndrome with eosinophilic symptoms are noted till now. So far, there is no data available on safety profiles in special populations like pregnant women, geriatric, and patients with hepatic & renal impairment. (3) Although data is available on the general adult population with rhinitis and asthma which are short-term studies, and no long-term studies are available. Only two long terms studies are done upto now, which are related to improvement in asthma and not on Rhinitis. The current study focuses on the safety profile of fluticasone as part of the maintenance therapy for Rhinitis (both Vasomotor & Allergic) at Government Tertiary Hospitals in India. (4)

Azelastine (0.1% w/v) is a potent long-acting antihistamine used in seasonal allergic rhinitis and perennial allergic rhinitis with patients aged above 6 years of age. (5-9) Dose formulations and strength are 0.14ml in each nostril twice daily is sufficient for therapeutic benefits. No data is available on usage in the geriatric population. Strictly avoided in patients below 6 years of age. Although teratogenicity has been established with azelastine usage in animal studies, but it was confined to oral use because azelastine nasal formulation has poor systemic absorption and is very less likely to cause/induce reproductive toxicity or teratogenicity. The most common ADR reported with azelastine is nausea and dysgeusia. (10-14)

DUONASE is an intranasal spray that is a combination of azelastine hydrochloride and fluticasone propionate. The spray contains micronized fluticasone and aerosolized azelastine which delivers about 50mcg of fluticasone and 140mcg on each spray or each breath. Every person should be advised about the priming of nasal spray before intake spraying into each nostril. Special caution should be given to the elderly or patients who are regular alcohol drinkers or psychiatric patients receiving anti-depressants because of the risk of motor impairment.

MATERIALS AND METHODS:

We carried out a prospective observational study on the safety profile of DUONASE users; who used it for atleast a period of 6 weeks after the initiation of therapy with duonase. The study data was collected during the period of June to July 2022(i.e., 2 months). A total of 140 Allergic Rhinitis patients were screened for selection into our study as a data source. All participants are instructed to use the nasal spray DUONASE twice daily without missing the dose by the ENT department physicians to achieve complete resolution of symptoms. The total compliant patients are verbally investigated for ADRs and we have cross-checked the ADR monitoring data along with data from

ENT physicians who were consulted by the patients who have experienced minor adverse effects. Then all the data from the ENT department of our institute was collected and collated with MS – EXCEL 2019 to determine the incidence of side effects or ADRs related to DUONASE nasal spray. The study was approved by the Institutional Ethical Committee of our institute and the participant's confidentiality was guaranteed. The selected patients are advised to appear in ENT OPD weekly once without fail to note side effects if any. Patients without any concomitant systemic diseases or any immunological disorders which are not going to interrupt the study results are included in the study.

Gross Examination of the Ear, Nose, and Throat of the patients:

The history of the present illness is taken thoroughly. A complete examination of the ear, nose, and throat are to be done on every subject even if there are no other complaints reported.

Past and Personal History:

Each person was asked about the history of any illness and its treatment followed by their personal habits like smoking/ chewing tobacco, alcohol consumption, etc.

Procedure for examination of Ear:

The person to be tested was asked to sit in front of the examiner. External meatus and tympanic membranes are examined with the aid of an otoscope to observe any signs of infection, inflammation, or any other findings like skin erosion and other abnormal findings. A complete nasal examination is done by using a nasal speculum. The throat is examined with a direct laryngoscopy technique. In non-anesthetized patients, an otoscope cone of the proper diameter is gently inserted into the vertical ear canal. Once the ear canal lumen is centered in the eyepiece, the otoscope cone is advanced deeper into the ear canal. This technique avoids the painful scraping of the sides of the ear canal. Using an otoscope, the tympanic membrane is examined thoroughly to observe any discharge, pus, or local inflammation. Routine tympanometry was done to rule out middle ear defects.

Procedure for examination of Nose:

Complete nasal inspection is to be done by observing the anterior, lateral surfaces of the nasal bridges. Skin changes on external and internal surface of the nose is to be examined to identify skin lesions like basal cell carcinoma or any localised inflammatory conditions. Examination of the nasal cavity through nasal speculum to identify any changes in nasal mucosa and also to look after any deviations in nasal septum. Palpation of both nasal bones and nasal cartilage for irregularities and tenderness to exclude any abnormalities like polyps and sinusitis. Diagnostic Nasal Endoscopy is to be done when necessary.

Procedure for examination of Throat:

Oral cavity examination is to be done by examining the colour and moistness of oral soft tissue, odour of the breath. Indirect laryngoscopy is to be done for assessment of internal structures. External examination is to be done thoroughly to look for any lymphadenopathy.

RESULTS:

Out of 140 DUONASE users selected for the current study, 41 (29.28%) of the total population were having side effects [Table: 1].

Table 1: Prevalence Of Side Effects Among Duonase Users

Age group in years	*Users selected*	*Subjects with side effects*
21-30	28	5(3.5%)
31-40	16	11(7.85%)
41-50	55	11(7.85%)
51-60	30	9 (6.42%)
>60	11	5 (3.5%)
Total	140 (100%)	41 (29.2%)

The occurrence of somnolence was not detected in any one of the DUONASE users. Out of 41 DUONASE users with side effects, 11 (26.8%) reported cough, 20 (48.7%) reported headache, 09 (21.9%) reported dysgeusia, and 01(2.43%) had mild epistaxis. All the side effects listed are depicted in [Table: 2]. Irrespective of side effects, 44 DUONASE users had hyperacidity even since intranasal therapy began.

Table: 2 Side Effects List According to The Order of Frequency.

Side effects	*No of recorded reports*
Headache	20
Cough	11
Dysgeusia	9
Epistaxis	1

DISCUSSION:

In general, Clinical Data on Azelastine + Fluticasone combinations usage was confined to mostly white ethnic groups and very less data was available on the Asian population. The current study was conducted, and the data was analyzed to get an idea about side effects or adverse events patterns in Asian people particularly in India with DUONASE use which was done at a government tertiary care centre. The results of the study showed that the highest incidence rate(45%) of side effects was seen among the age group of >60 years. The least incidence rate (17.8%) of side effects was seen among the age group of 21-30 years. The highest prevalence rate of side effects was seen in age groups [31- 40 years] & [41-50 years], which was 11% in both age group's sample populations. None of the users in any age group had daytime somnolence. The percentage of DUONASE users with side effects as obtained from our study was 29.28% [Figure 1]. On contrary to this, the percentage of DUONASE users with side effects from similar studies is 2.71% among the total study participants of 405, which was a long-term study conducted in 2014 in UK with the same drug combination. (15) Our study data reveals that the magnitude of side effects among DUONASE users in India is much higher and it also shows the need for stringent medical check-ups to detect side effects in Indian DUONASE users. The majority of the patients reported headaches as their adverse effect and next following highly reported side effect was cough. (16-19) Moreover, many of them are unaware of having side effects, they tried to attend follow-ups regularly, even with side effects. They received continuous motivation regarding attending regular clinical OPD follow-ups. We also observed that regular visits to Government Tertiary Hospitals for follow-up were taboo among rural people using intranasal spray despite of illness and side effects; this behaviour was expressed only due to lack of knowledge and awareness among rural people towards health. (20-22) According to the latest literature, many studies have concluded that dysgeusia and epistaxis are highly reported side effects with long-term usage of DUONASE. Our data results were a bit different, this may be due to genetic differences in ethnicity among the study population because all the participants are confined to one specific region of India which was located in Southern Asia. But literature that we have considered as reference data was collected from USA, UK and Japan.

CONCLUSION:

The data obtained from the above study participants revealed that the most commonly reported side effect is headache. The order of frequency of ADR in our region or area who are Indian ethnic people: headache > cough > dysgeusia. This indicates ethnicity plays an important role in determining the safety profile of a drug. We can't determine or conclude the most

common ADR type and the incidence with this small observational study having a limited population.

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REFERENCES:

1. Carr W, Bernstein J, Lieberman P, Meltzer E, Bachert C, Price D, Munzel U, Bousquet J. A novel intranasal therapy of azelastine with fluticasone for the treatment of allergic rhinitis. Journal of Allergy and Clinical Immunology. 2012 May 1;129(5):1282-9.
2. Hampel FC, Ratner PH, Van Bavel J, Amar NJ, Daftary P, Wheeler W, Sacks H. Double-blind, placebo-controlled study of azelastine and fluticasone in a single nasal spray delivery device. Annals of Allergy, Asthma & Immunology. 2010 Aug 1;105(2):168-73.
3. Klimek L, Bousquet J, Price D. Safety evaluation of MP29-02 (a novel intranasal formulation of azelastine hydrochloride and fluticasone propionate) for allergic rhinitis. Expert Opinion on Drug Safety. 2016 Jan 2;15(1):117-29.
4. Krishnakumar D, Faizal B, Nair AS. Comparison of the Effects of Azelastine and Fluticasone Nasal Sprays in the Treatment of Allergic Rhinitis. *Indian J Otolaryngol Head Neck Surg*. 2022;74(Suppl 2):1632-1637. doi:10. 1007/s12070-021-02686-7
5. Watts AM, West NP, Smith PK, Zhang P, Cripps AW, Cox AJ. Nasal immune gene expression in response to azelastine and fluticasone propionate combination or monotherapy. Immunity, Inflammation and Disease. 2022 Mar;10(3):e571.
6. Glenis S, Stephen D.Allergic Rhinitis. In Michael G, George GB editors Scott-Brown's Otolaryngology, Head and Neck Surgery.7th edition Great Britain: Hodder Arnold 2008, Vol 2. P.1386-1407.
7. Meltzer EO. Quality of life in adults and children with allergic rhinitis. Journal of Allergy and Clinical Immunology. 2001; 108(1):45-53.
8. Chandrika D. Allergic rhinitis in India: an Overview. International Journal of Otorhinolarynglogy Head and Neck Surgery. 2017; 3(1):1-6.
9. Hansen J, Klimek L, Hormann K. Pharmacological management of allergic rhinitis in elderly: safety issues with oral antihistamines. Drugs Aging. 2005; 22: 289-296.
10. Bousquet J, Van Cauwenberge P, Ait Khaled N et al. Pharmacologic and anti-IgE treatment of allergic rhinitis ARIA update. Allergy. 2006; 61: 1086-1096.
11. Strokes M, Amorosi SL, Thompson D et al. Evaluation of patients preferences for Triamcinolone acetonide aqueous, Fluticasone propionate and Mometasonefuroate nasal spray in patients with allergic rhinitis. Otolaryngology Head and Neck Surgery. 2004; 131: 225-231.
12. Bernstein JA. Azelastinehydrochloride: a review of pharmacology, pharmacokinetics, clinical efficacy and tolerability. Current Medical Research and Opinion. 2007; 23: 2441-52.
13. Bousquet J, Khaltaev N, Cruz AA et al .Allergic rhinitis and its impact on asthma (ARIA). Allergy. 2008; (86):8–160.
14. Barnes PJ. Pulmonary pharmacology. In: Brunton LL, Dandan RH, Knollmann BC editors. Goodman and Gilman's Pharmacological Basis of Therapeutics. 13thed. New York
15. Skidgel RA. Histamine, Bradykinin and their antagonists. In: Brunton LL, Dandan RH, Knollmann BC editors. Goodman and Gilman's Pharmacological Basis of Therapeutics. 13thed. New York
16. Varshney J, Varshney H. Allergic Rhinitis: an Overview. Indian Journal of Otolaryngology Headand Neck Surgery 2015; 67(2):143-149.
17. Ratner P, Sacks H. Randomized double blind trial of Azelastine nasal spray plus Fluticasone nasal spray compared to either agent alone in patients with allergy to Texas Mountain Cedar. Annals of Allergy Asthma and Immunology. 2008; 100(1):74-81.
18. Hampel FC, Ratner PH, Van Bavel J. Double blind placebo controlled study of Azelastine and Fluticasone in a single nasal spray delivery device. Annals of Allergy Asthma and Immunology 2010; 105(2):168-73.
19. Behncke VB, Alemar GO, Kaufman DA, et al. Azelastine nasal spray and Fluticasone nasal spray in treatment of geriatric patients with rhinitis. Journal of Allergy and Clinical Immunology 2006; 117-263.
20. Sami AS, Ahmed N, Ahmed S. The effect of novel combination therapy with Azelastine hydrochloride and Fluticasone propionate in Allergic Rhinitis. Otolaryngology 2016; 6(4)1-8.
21. Dhanush HC, Malashetti S, Chandrashekharayya SH,KhavasiP. Comparative study of fluticasone propionate combined with azelastine versus fluticasone propionate alone as nasal spray in allergic rhinitis. International Journal of Otorhinolaryngology Head Neck Surgery 2021; 7:487-92.
22. Salib JR, Howarth PH. Safety and tolerability profiles of intranasal antihistaminic and intranasal corticosteroids in treatment of allergic rhinitis. Drug Safety 2006; 26:863-93.