COMPARATIVE STUDY OF EFFICACY AND SAFETY OF INTRANASAL AZELASTINE HYDROCHLORIDE AND FLUTICASONE FUROATE IN TREATMENT OF ALLERGIC RHINITIS

BY

Dr. NANDISH C, MBBS

Dissertation submitted to the

Sri Devaraj Urs Academy of Higher Education and Research,

Tamaka, Kolar, Karnataka

In partial fulfillment of the requirements for the degree of

DOCTOR OF MEDICINE
IN
PHARMACOLOGY

Under the guidance of

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April 2014

Sri Devaraj Urs Academy of Higher Education and Research
Tamaka
Kolar

Declaration by the candidate

I hereby declare that this dissertation entitled **"COMPARATIVE STUDY OF EFFICACY AND SAFETY OF INTRANASAL AZELASTINE HYDROCHLORIDE AND FLUTICASONE FUROATE IN TREATMENT OF ALLERGIC RHINITIS"** is a bonafide and genuine research work carried out by me under the direct guidance of **Dr. SARALA. N, MD,** Professor and Head, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar.

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This is to certify that, the ethics committee of Sri Devaraj Urs Medical College, Tamaka, Kolar has unanimously approved the dissertation work of **Dr. NANDISH C**, a postgraduate student in the department of Pharmacology, Sri Devaraj Urs Medical College entitled "**COMPARATIVE STUDY OF EFFICACY AND SAFETY OF INTRANASAL AZELASTINE HYDROCHLORIDE AND FLUTICASONE FUROATE IN TREATMENT OF ALLERGIC RHINITIS"** to be submitted to the Sri Devaraj Urs Academy of Higher Education And Research, Tamaka, Kolar.

MEMBER SECRETARY **PRINCIPAL**

ACKNOWLEDGEMENT

This would have not been possible without the help of few kind hearted people. I thank all those who have directly and indirectly contributed their knowledge in bringing out this research work.

No words can express my gratitude to Dr. Sarala N, Professor & HOD, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar. Her everlasting immense enthusiasm in teaching, unimaginable store of knowledge and her graceful blessings will definitely lead a student towards a bright future. I will be thankful to her for the rest of my career.

The other two wonderful people whom I should not forget for their immense moral as well professional support are Dr. Kumar. T. N and Dr Nagesh Raju. G. Dr Kumar. T. N, former Professor and HOD, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar is a person beyond any comparison. I can only say that he is my role model teacher and I need his blessings throughout my lifetime and thank him for all his support.

Dr. Nagesh Raju. G, former Professor, Department of Pharmacology, Sri Devaraj Urs Medical College, Tamaka, Kolar was instrumental in me preparing the synopsis and his excellent views and ideas towards guiding students has impressed me in selecting this work.

I express my humble and sincere respect to my co-guide Dr. Azeem Mohiyuddin S M, Professor & HOD, Department of Otorhinolaryngology, Sri Devaraj Urs Medical College, Tamaka, Kolar who guided me in completing this dissertation. I also thank Dr. Nikhil Bharadwaj, Associate Professor, Department of Otorhinolaryngology, Sri Devaraj Urs Medical College, Tamaka, Kolar for his immense help during my study.

I thank Dr. Girish M Bengalorkar, former Associate Professor, Department of Pharmacology for guiding me in making the statistical analysis. And not forget Dr. Bhuvana. K, Associate professor, Department of Pharmacology for sparing her valuable time and helping me in bringing out this dissertation. I also thank Dr. Smitha Rai, Dr Meenakshi L, Dr. Jayakumar J K and Dr. Asha B, Assistant professors in Department of Pharmacology for their encouragement and support.

I immensely thank my colleagues Dr Dharmistha Patel and Dr Tejashree T who helped me out at every level in completing my dissertation. I also thank Dr Dheepan Nayagam B, Dr. Revathi Ramesh, Dr Chetan Kumar G, Dr Ganashree P, Dr. Varadaraju and Dr Ashwitha Shruthi Dass, the postgraduate colleagues in the Department of Pharmacology for their valuable feedback and support. And last but not the least I thank all the non teaching staff of Department of Pharmacology for bearing with me and helping out in carrying out this dissertation.

Finally, I thank my beloved parents, brother and sister for their surplus cooperation and encouragement which resulted in shaping this dissertation work and not to forget I thank the Almighty for conferring in me the confidence, skill and ability to make this work a success.

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TABLE OF CONTENTS

List of Tables

List of figures

INTRODUCTION

Every organ system in the human body is capable of producing an immunologic response and therefore, is capable of developing allergic dysfunction and clinical disease. Allergic rhinitis, is a common disease, marked by rhinorrhoea, nasal obstruction, nasal itching and sneezing.[1] It is increasing worldwide and has major effect on health related quality of life. It is associated with development of sequelae such as chronic rhinosinusitis, nasal polyp, serous otitis media, bronchial asthma, orthodontic problems and other ill effects of prolonged mouth breathing, especially in children. Allergic rhinitis occurs following an initial sensitization phase, in which allergen comes in contact with nasal mucosa resulting in antibody (IgE) formation and development of atopy. Subsequently, depending upon the level of exposure and degree of sensitization, allergen can then trigger a humoral response, manifested by symptoms. Allergic rhinitis occurs in atopic individuals who are exposed to common aeroallergens, it is either seasonal or perennial. Although frequently trivialized by patients and doctors it remains a common cause of morbidity, social embarrassment and impaired performance either at school or in the workplace.[2]

There are three modalities of treatment of allergic rhinitis – allergen avoidance, pharmacotherapy and immunotherapy. Avoidance of allergen triggers is as an important step in obtaining symptomatic relief but is often impractical. Antigens are not always avoidable and immunotherapy modifies the allergic response but does not always afford protection from an overwhelming antigen exposure. Therefore, symptomatic management by means of pharmacotherapy is required to some degree for every patient with allergic rhinitis. In recent years, the mainstay has been the use of topical corticosteroid and non-sedating

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antihistamines and which among this should be used as the first line drug for treatment of allergic rhinitis has been a matter of discussion from several years

Anti-histamines were the first effective drugs to be used for symptomatic relief of allergic rhinitis. The main drawback of this drug was its sedative effect. Antihistamines act to control the "wet" symptoms of allergic rhinitis such as rhinorrhea, sneezing and itching. Second generation or non-sedating antihistamines e.g. loratidine, cetirizine, desloratidine, levocetirizine, mizolastine have multiple actions including direct effects on allergic mediators. They do not cross the blood-brain barrier, so do not produce sedation.. A newer generation includes (e.g. livostin, azelastine) used topically have said to have fewer side effects but increased effectiveness.[3]

On the other hand, appreciation of effectiveness of nasal steroid sprays in relieving nasal symptoms of allergic rhinitis has grown steadily over last several years, including relief of sneezing, congestion, nasal pruritus, and allergic eye symptoms. Intranasal atomized sprays eliminate the systemic side effects and equal or exceed the efficacy of their oral counterparts.[4] According to management of moderate – severe allergic rhinitis adapted by ARIA (Allergic rhinitis and its impact on asthma) guidelines, antihistamines or intranasal corticosteroids are first line of treatment.

Hence, this study was taken to clinically evaluate the efficacy and safety of intranasal azelastine hydrochloride with intranasal fluticasone furoate in treatment of patients with allergic rhinitis

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OBJECTIVES OF THE STUDY

- To study the efficacy of intranasal Azelastine hydrochloride and Fluticasone furoate in allergic rhinitis
- To study the safety profile of Azelastine hydrochloride and Fluticasone furoate in allergic rhinitis
- To determine the cost incurred with the use of the above drugs in allergic rhinitis patients

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REVIEW OF LITERATURE

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Historical aspect

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Historically, allergic reaction has been known for over 150 years.[5] Classical symptoms of allergic rhinitis were described as early as 1819 by John Bostock of England. The term allergy was coined and described as "*any form of altered biological reactivity*" by an Austrian Paediatrician – Clemens Vonpirquet in 1906. He identified that his own "Summer Catarrh" of sneezing, itchy eyes, and nasal congestion occurred only during summer months.[6] In 1928, he assessed his symptoms of allergic rhinitis with cutting of hay and deduced his problems were related in some way to substances emanating from hay. Thus coined the term "Hay fever".[6] Although prime target cells of allergic reaction, mast cell, were described in 1877 by Paul Ehrlich, significance of degranulation and release of vasoactive amines were not described until 1940s.[7] In 1865, Blakley performed a scratch test on himself to show his sensitivity to eye grass and in early 1900s Scratch test were commonly used to diagnose immediate type of allergy.[8]

In 1921, Prausnitz and Kristnes described passive transfer of small amount of serum of an individual afflicted with allergic rhinitis to skin of non-sensitized individual and discovered that it produced a wheal. This demonstrated an "allergic factor" within blood of affected donor.[7] In 1960s, Benaich and Johansson in Sweden, independently identified a protein component of myeloma protein called "ND protein". In conjunction with L Wide, they identified this substance as globulin IgE and established it as factor responsible for production of allergic symptoms.[6] Skin prick or puncture test was developed by Lewis and Grant in 1924 but did not gain widespread acceptance until its modification by Pepys in 1975.[8]

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Histamine was originally identified by Sir Henry Dale in 1910.[9] In 1937, first histamine receptor antagonist was discovered by Staub and Bovet – received Nobel Prize for physiology and medicine in 1957.[10] In 1981, Terfenadine was introduced as first oral non-sedating anti-histamine for treatment of allergic rhinoconjunctivitis.[11] Beclomethasone, first topical corticosteroid for treatment of seasonal allergic rhinitis was introduced in 1973 as nasal spray.[12]

NASAL PHYSIOLOGY AND FUNCTIONAL ANATOMY

External nose is shaped by nasal bones, upper and lower lateral cartilages wrapped by skin and facial muscles in prolongation of nasal bony pyramid. Internal nose mainly consists of bony framework covered with respiratory mucosa. The nasal septum divides the nasal cavity into two sides and is composed of cartilage and bone. Only first few millimeters are covered by skin (vestibule). Continuous slow growth of septum upto age of 15 might explain frequently observed septal deviations in adults, leading to some degree of nasal obstruction.

From aerodynamic point of view, nose may be divided into

- Vestibule lined with stratified squamous epithelium.
- Nasal valve accounting for 50% of total resistance to respiratory airflow, ~~is~~ approximately 3 cms into the nostrils.
- In the nasal cavity inferior, middle, and superior turbinate are located, lined with pseudostratified columnar ciliated epithelium. The turbinates increase mucosal surface to about 150 to 200 cm^2 and facilitate humidification, temperature regulations and filtration of inspired air.[13]

The two nasal bones together with the two upper and lower lateral cartilages form the external framework of the nose.[14] Although the nose is a paired structure, divided sagitally into two chambers it acts as a functional unit.[15] The nasal septum is a midline

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structure derived from several bony and cartilaginous sources: superiorly and posteriorly by the perpendicular plate of ethmoid bone and vomer and anteriorly by the septal (quadrilateral) cartilage, premaxilla, and membranous columella. Inferiorly, it is formed by the crests of the vomer, maxillary and palatine bones and posteriorly by the sphenoidal crest. The palatal processes of the maxilla and horizontal processes of the palate bones from the floor of the nose. The roof of the nose is formed by alar cartilages, the nasal bones, the nasal processes of the frontal bones, and the bodies of the ethmoid and sphenoid bones. The cribriform plate forms the major portion of the roof of the nasal lumen. The inner surface of the maxillae, the lacrimal bones, the superior and middle turbinates, the inferior turbinate and the medial pterygoid plate make up the lateral wall. The large, tortous, valveless, anastomosing veins, called sinusoids are found mainly in the middle and inferior turbinates. By the degree of fluid contained in the sinusoids, they can influence the size of the nasal airway and, in effect are capacitance structures. They respond to neural, mechanical, thermal, physiologic and chemical stimuli.[14]

The major site of airway resistance in approximately 3 cm into nostrils at the anterior end of inferior turbinate. This flow-limiting site is termed nasal valve and is critically dependent as status of engorgement of venous sinusoids within the inferior turbinate. At this site, airflow changes from laminar to turbulent. Turbulent airflow facilitates mixing, warming and humidification of inspired air and also assists with particle deposition by inertial impaction.[16]

Airway:

The nose provides a semirigid passage for air movement, as it enters it is directed upward by the nares. The air stream turns to 80 to 90 degrees posteriorly as it reaches the nasal vault to

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traverse a mostly horizontal path until it impacts against the posterior wall of nasopharynx. At this point, joined by the airstream from other side, an 80 to 90 degree downward bend occurs. Each of their two bends termed "impaction points" facilitates the removal of particules contained in the incoming air. Impaction against the adenoid may enable the adenoid to respond immunologically by "sampling" the contaminants contained in the air.

Air stream :

The anterior nasal valve or ostium internum, is located at the lumen nasi, some 1.5 to 2 cm posterior to the nares. At this point, the cross-section of the airway is 20 to 40 mm^2 on each side, is the narrowest part of the upper respiratory tract and provides about 50% of the total airway resistance. Particles of approximately 5 µm aerodynamic equivalent diameter (AED) or greater are removed by the nose and nasopharynx. Smaller particles penetrate to varying degrees to the lower respiratory tract. Virus containing droplets coalesce into diameters, frequently exceeding 5 to 6 µm, and thus are largely retained in the nose.

Air condition training:

The air is heated (or cooled) by radiations from the mucosal blood vessels. Humidification occurs by evaporation from the mucous blanket. Hence the inspired air is near normal body temperature and the relative humidity is near 100%. The mucosal blood vessels lie in two layers of more or less parallel rows. The more superficial layer sends capillaries into the epithelium, and the capillaries of the deeper layer near the basement membrane are fenestrated to

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facilitate fluid movement. The flow of blood is from posterior to anterior, opposite to the flow of inspired air and mucus. The mechanism of a "counter current" adds to the efficiency of the system.[14]

Nasal secretions:

Nasal secretions are composed of two elements, glycoproteins and water with its proteins and ions. The glycoproteins are produced by mucus glands and the water and ions from the serous glands and also indirectly from transudation from the capillary network. The nasal mucus film is two layers, an upper more viscous layer, and a lower more watery layer in which the cilia can move freely. Glandular mucus and goblet cells contain large secretary granules. These granules contain neutral glycoproteins, enzymes such as lysozymes and lactoferrin as well as immunoglobulins of the IgA class.[15]

Composition of mucus:

Although some of the water, ions and enzymes may come from outside the nose (tears), the majority are produced in the nasal cavity. The watery layer in mucus merges gradually into more viscous upper layer. It is however, more practical to consider mucus as two layers, a sol layer and a gel layer. The gel layer contains more of the glycoproteins from which many of the properties of mucus are derived. Glycoproteins give mucus, its two most commonly measured properties, viscosity and elasticity.[17] The mucus blanket functions as a lubricant, protects against desiccation and traps particulate matter and soluble gases. It amounts to 1 to 2 liters per day.[14]

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Histology:

Nasal mucosa consists of three layers - ciliated-epithelium, basement membrane, lamina propria or submucosa. Three types of cells are identified within the epithelium - basal cells, goblet cells, ciliated or non-ciliated columnar cells, which are all attached at basement membrane. They also adhere to neighbouring cells forming epithelial barrier. Submucosa contains cellular components, serous and seromucous glands, nerves and complex vasculature. The density of goblet cells in nose and in large airways is approximately10,000/mm^2.[18] There is an enhancement in mucus discharge from inferior turbinate goblet cells of patients with perennial allergic rhinitis, attributed to a non-hyperplastic increase of nasal goblet cells functional activity. Anterior serous glands consist of 200 purely serous glands located at entrance of nose. Small seromucous glands are present in submucosa of nasal mucosa. After birth, the density of nasal glands decreases constantly. At birth, number of glands in nose reaches a maximum of 34 glands/mm^2, while there are 8.3 glands/mm^2 in adult nose. These differences may explain why rhinorrhoea is common in infants and children. Total number of glands in nose is approximately 1, 00, 000.[18] Mucociliary transport is dependent on viscosity of mucus and on effective movement of cilia, moving superficial gel layer and debris trapped therein at a speed of about 3 to 25 mm/min simulating conveyor belt mechanism. Viral or bacterial infections as well as allergic inflammation have been shown to heavily decrease or abrogate mucociliary clearance.[19] When airborne allergen particles are inhaled through the nose, the majority of particles larger than 5 mm in size are deposited on surface of nasal mucosa and then

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transported from nose to pharynx within 15-30 minutes. However, water-soluble antigenic substances are eluted from particles and may be absorbed quickly by nasal mucosa.[13]

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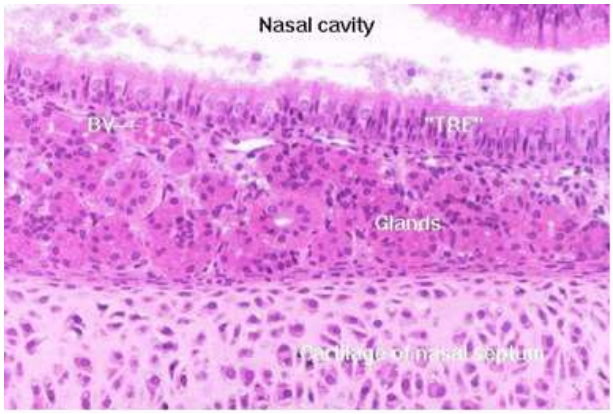

Figure -1 histology

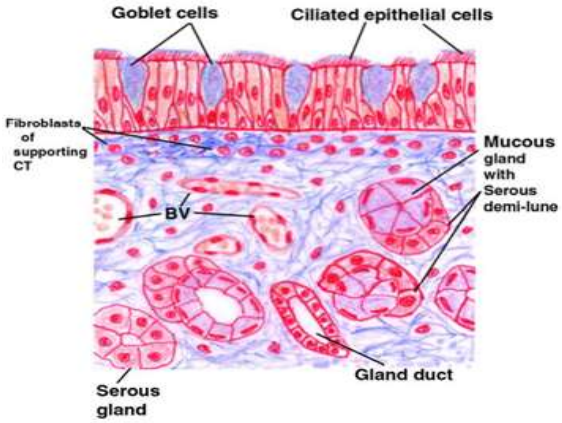

Figure -2 histology of nose

Nasal microvasculature

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Microvasculature of nose consists of dense subepithelial network of capillaries with fenestrations between endothelial cells. This network provides nutrients to epithelium and glands and allows passage of water into lumen for evaporation and air conditioning. Arteriovenous anastomoses, allow rapid passage of blood through mucosa. They are probably important in air conditioning and in counter current mechanisms. A system of capacitance vessels or sinuses which, when they distend, block nasal lumen and when they empty, open nasal passages. Changes in their volume will affect the filtering and air conditioning functions of nose. The arteries are surrounded by smooth muscle layer that controls blood supply into venous sinusoids, also referred to as capacitance vessels. The nasal mucosa can shrink or expand rapidly by changing blood volume in response to neural, mechanical, thermal or chemical stimuli. In normal conditions, there is rhythmic alternating congesting and decongestion of mucosa, referred to as nasal cycle.[20]

Nervous system of nose

Nerves present in nasal mucosa include cholinergic nerves and nerves of nonadrenergic, non-cholinergic systems. Neurotransmitters and neuropeptides released within autonomic nervous system exert haemostatic control of nasal secretion. Parasympathetic nerve stimulation induces glandular secretion, which is blocked by atropine and causes vasodilatation. Sympathetic nerve stimulation causes vasoconstriction and thus decreases nasal airway resistance. Peptides from sensory nerves such as calcitonin related peptide, substance P; and neurokinin A are suspected to play a role, both in normal

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subjects and allergic patients, in vasodilatation, plasma extravasation, neurogenic inflammation and in mast cell nerve interactions.[21]

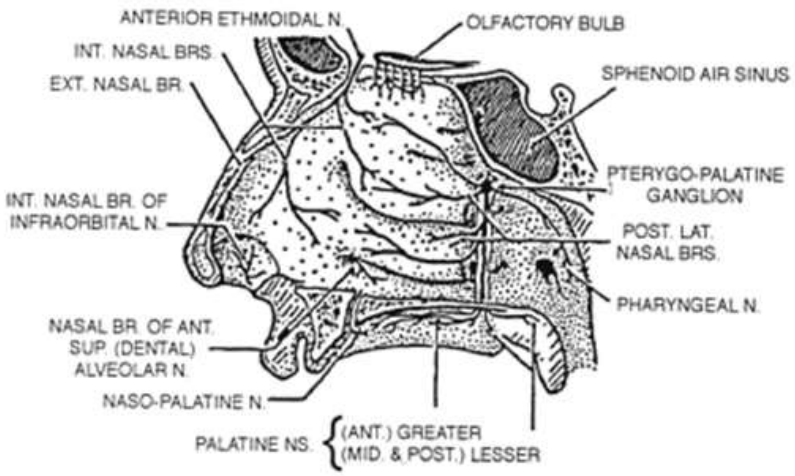

Figure 3; Nervous supply of nose

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IMMUNOLOGY[13]

Immunology is the study of the immune system and has its historical foundations in the way the body combats infectious disease. Long before the principles of microbiology and immunology were understood, it had been recognized that not all individuals became ill during an epidemic, and that those who recovered were resistant to future outbreaks. This state was termed immunity, meaning exemption.

The immune system consists of a number of organs and several different cell types. All the cells of the immune system, tissue cells and white blood cells are leukocytes develop from pleuripotent stem cells in the bone marrow. The production of leukocytes is through two main pathways of differentiation. The lymphoid lineage produces T – lymphocytes and B – lymphocytes while the myeloid pathway gives rise to mononuclear and poly morphonuclear leukocytes as well as platelets and mast cells.

Any immune response involves, firstly, recognition of the pathogen or other foreign material, and secondly, mounting a reaction against it to eliminate it, which is mediated by a variety of cells, and by the soluble molecules which they secrete, like lymphokines and cytokines. Damage to the surrounding tissues during the course of an immune response may sometimes exceed the potential benefits. Such exaggerated responses are termed hypersensitivity reactions

Immunity can be broadly classified into two types. Those where prior exposure to the particular organism enhances a second immune response (immunological memory),

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namely specific, acquired or adaptive immunity, and those, which are only minimally affected namely non-specific, innate or natural immunity.

Innate immunity

A variety of factors contribute to innate immunity like physical barrier provided by skin and mucous membranes.

- The cilia of the respiratory system and the motility of the gastrointestinal tract.
- Lactoferrin in saliva, lysozyme in saliva, nasal secretion and tears.

If a potentially pathogenic organism breaches the external barrier and enters the blood, two vital second lines of non-specific defense are provided by phagocytic cells and the complement system.

Phagocytosis involves the recognition, engulfment, killing and digestion of particulate matter. The latter may be whole cells or debris, and of foreign or host origin, phagocytes are thus not only defenders but also scavengers. The task is principally undertaken by two morphologically distinct populations of bone marrow derived leukocytes – Neutrophils and monocyte – macrophages.

The complement system consists of a series of glycoproteins that circulate in the extracellular fluid compartment. They participate in a triggered enzyme cascade, which comprises an initiation phase, amplification, and the assembly of a membrane attack sequence, which can be brought about by two major pathways:

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- Classical pathway and
- Alternative pathway

Biologically, the triggering of the complement cascade by either pathway leads to the activation of cells, opsonization and the lysis of complement-coated cells.[22]

Acquired immunity

Acquired immunity responses have the following characteristics

- They show memory – initial exposure to an infectious organism leads to a primary response, encountering the organism again produces an accelerated secondary response, encountering the organism again produces an accelerated secondary response which persists.
- They show specificity – the development of resistance following exposure to one organism does not confer resistance to unrelated organisms.
- They can be divided into responses, which are mediated by humoral factors

(Antibodies), and those mediated by specifically sensitized cells.[22]

Hypersensitivity reactions

As already stated, an exaggerated or inappropriate immune response, which damages host tissues, is termed a hypersensitivity reaction.[22] Immunologic mechanisms of hypersensitivity are based on Gell and Coomb's classification (1975).

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Type I: Immediate hypersensitivity

- Antigen binds to 2 molecules of IgE or IgG attached to the receptor site (Fc) on the surface of a basophil or a mast cell.
- This is followed by a release of chemical mediators: histamine, serotonin, bradykinins, leukotrienes, eosinophil chemotactic factor, which ultimately result in vasodilatation and increased vascular permeability as well as bronchoconstriction.
- Examples: allergic rhinitis, bronchial asthma, and anaphylactic shock.

Type II: Cytotoxic antibody (Ig G, Ig M)

- IgG or IgM binds to the cell surface bound antigen-activating complement, which leads to lysis or agglutination of the target cell.
- Examples: hemolytic anaemia, hemolytic disease of the newborn.

Type III: Immune Complex

- Antigen–antibody complex combines with complement to form immune complexes, these deposit in the tissue.
- Vasoactive amines are liberated and inflammation of the involved tissue occurs.
- Examples: autoimmune disease, serum sickness, some types of nephritis.

Type IV: Delayed hypersensitivity

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- Sensitized T-cells (Lymphocytes) cause target cell injury or death by direct cell attachment or release of mediators.

- Examples: Contact dermatitis, graft and tumour rejection.[5]

-

Mast Cells

Granule laden mast cell was discovered by Paul Ehrich in 1879. They are devised form CD_{34+}, haemotopoietic progenitor cells which migrate to and mature in peripheral tissue.[23] Mucosal and connective tissue mast cells are distributed throughout the nasal mucosa in approximately equal proportions. Mast cells degranulation has been demonstrated histologically following allergen provocation. Number of mast cells increase within the epithelium during pollen season. When activated by an IgE – dependent or independent mechanism, mast cells release:-

- Histamine and granule proteins such as tryptase, by degranulation.

- Arachidonic acid metabolites including Cys LT by activation of membrane phospholipids.

- Cytokines – These are present in mast cells as preformed mediators.

When mast cells are activated via high affinity IgE receptor (Fc) a release of several cytokines has been observed. These include Th2 cytokines such as IL-4, IL-5, IL-13 and pro inflammatory cytokines such as IL-6, IL-8, IL-10 and α TNF. The release of Th2 cytokines

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by mast cells may be of great importance of IgE immune response. It has been shown that nasal mast cells can induce synthesis of IgE.[24]

Eosinophils

The eosinophil granulocyte was first observed by Wharton Jones in 1846, in the unstained preparations of peripheral blood. The term "EOSINOPHIL" was so named by Paul Ehrlich in 1879 because of the intense staining of its granules with the acidic dye eosin. The first person to take interest in the nasal cytology was Charles Eyennan in 1927. Later on Hansel (1934), Walsh and Lindsay (1934), Bryan (1959) studied the value of cytology. Eosinophils progenitors can be found in nasal mucosa in seasonal allergic rhinitis and in nasal polyi. Within the tissue, eosinophils mature and stay alive for several days or even weeks. They are associated with asthma, cutaneous and parasitic disease as bystander cells. Mature eosinophils are easily recognizable by their bi-lobed nucleus and specific granules. Eosinophils synthesize and release cytokines such as IL-3, IL-5, GM-CSF, Chemokines and TGF – B. Eosinophils express various membrane receptors for IgG, IgA and IgE. During late phase reaction following allergen challenge, eosinophils increase in number and release mediators. Eosinophils also increase in nasal epithelium and submucosa of patients with seasonal or perennial allergic rhinitis. On activation they increase vascular permeability and mucus secretion.[13]

T- lymphocyte

T-lymphocytes are mediators of cellular immunity and are essential for induction of humoral immunity to most naturally encountered antigens. T-lymphocytes are among the

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principal factors that regulate and co-ordinate immune responses in allergic disease. Th1 and Th2 are helper T-cell subsets.

Th1 T cells, which mainly release IL-2, are involved in delayed hypersensitivity immune reactions. Th2 T cells mainly release IL-4 and IL-5 and are involved in IgE mediated allergic inflammation. In atopy, Th2 cells are thought to regulate IgE synthesis and cell recruitment at sites of inflammation. Mucosal inflammation in allergic rhinitis is characterized by tissue infiltration of T- lymphocytes (CD4+ T cells and CD 25 + T cells) both in submucosa and epithelium. There is significant correlation between the increase in CD4 + T cells during the late phase allergic reaction following an allergen challenge and number of infiltrating eosinophils in mucosa.[13]

B-Cells

In bone marrow, B cells mature in close association with stromal cells, which interact by direct contact or via cytokines to induce differentiation. These mature cells will then migrate to secondary lymphoid tissues (spleen, tonsils and lymphnodes) and form part of re-circulating lymphocyte pool. B-Lymphocytes constitutes 10% to 20% of circulating lymphocytes. Upon antigenic stimulation B-cells form plasma cells that secrete immumoglobulins, are the mediators of humoral immunity. B-cells can be found in epithelium and lamina propira of nasal mucosa. They can undergo class switch to Ig E locally in nasal mucosa.[13]

IgE immunoglobulin

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It is the only immunoglobulin presents in trace amount in serum and secretions under normal conditions. The ratio of IgE to IgG is about 1: 40,000. IgE has special affinity for surface of mast cells and basophils. However only 0.01% of IgE is bound to basophils. 99.99% is found free in serum. IgE producing cells are mainly located in respiratory mucous membrane, GI tract and regional lymphnodes. The only known effect of IgE is that it mediates hypersensitivity, through release of vasoactive amines from mast cells. There is striking increase in serum concentration of IgE in patients with parasitic disease.[6]

Mechanism of type I hypersensitivity:

Type 1 hypersensitivity is a rapidly occurring reaction that follows the combination of an antigen with antibody previously bound to the surface of mast cells and basophils. Many type 1 reactions have two well defined phases. The initial response characterized by vasodilatation, vascular leakage and smooth muscle spasm, usually becomes evident within 5 to 30 minutes after exposure and tends to subside in 60 minutes. A second late phase reaction sets in 2 to 8 hours later without additional exposure to antigen and lasts for several days. This late phase reaction follows in only about 50% of individuals; it is characterized by increasingly intense infiltration of tissues with eosinophils, neutrophils, basophils and monocytes as well as tissue destruction in the form of mucosal epithelial cell damage.

In humans, type 1 reactions are mediated by IgE antibodies. The basic sequence of events in the pathogenesis of this form of hypersensitivity begins with the initial exposure to certain antigens (often called allergens). The allergen stimulates the induction of CD4+ T-cells. These CD4+ cells play a pivotal role in pathogenesis of type 1 hypersensitivity because the cytokines

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secreted by them cause IgE production by B-cells, act as growth factor for mast cells and recruit and activate eosinophils. Once IgE is bound to the surface of mast cells, the individual is primed to develop type 1 hypersensitivity. Re-exposure to the same antigen results in fixing of the antigen to cell-bound IgE, initiating a series of reactions that lead to the release of several powerful mediators that are responsible for the tissue changes and clinical features of type 1 hypersensitivity

Primary mediators :

Primary mediators or preformed mediators, are contained within mast cell granules. Histamine is the most important preformed mediator. It is known to cause increased vascular permeability, vasodilatation, bronschospasm and increased secretion of mucus. Other rapidly released mediators are factors that are chemotactic for neutrophils and eosinophils. Other mediators make up the granule matrix; they include heparin and neutral proteases (eg. tryptase).

Secondary mediators :

These include the two classes of compounds.

1.Lipid mediators 2. Cytokines.

Leukotrienes are extremely important in the pathogenesis of type 1 hypersensitivity. Leukotriene C4 and D4 are the most potent vasoactive and spasmogenic agents. Leukotriene B4 is highly chemotactic for neutrophils, eosinophils and monocytes. Prostaglandin D2 is the most abundant mediator derived by the cyclooxygenase pathway in mast cells. It causes intense bronchospasm as well as increased mucus secretion. Platelet activating factor (PAF) another secondary

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mediator, causes platelet aggregation, release of histamine and bronchospasm. It is also chemotactic for neutrophils and eosinophils, causing their accumulations and subsequent degranulation. Mast cells can produce a variety of cytokines, including TNF, IL-1, IL-4, IL-5 and IL-6. IL-4 and IL-5 initiates IgE synthesis. IL-4 is a mast cell growth factor.[25]

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ALLERGIC RHINITIS

Definition

Allergic Rhinitis is an IgE mediated hypersensitivity disease of the mucous membrane of nasal airway characterized by sneezing, itching, watery nasal discharge and sensation of nasal obstruction.[13] Allergic Rhinitis represents a global health problem. It is an extremely common disease worldwide affecting 10 to 25% of population.[13]

Age and Gender:

Symptoms of allergic rhinitis can begin at any age but most frequently reported in adolescence or young adulthood. Rate of prevalence are similar for males and females and no racial or ethical variations reported.[13] Incidence of developing allergic diathesis is higher in children whose parents suffer from allergic rhinitis. If one parent has allergy chance of child having are 29% and increase to 47% when both have the disease.

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Morbidity[8]

While allergic rhinitis itself is not life threatening (unless accompanied by severe asthma or anaphylaxis), morbidity from the condition can be significant. It often co-exists with asthma and may be associated with its exacerbations. It leads to otitis media, eustachian tube dysfunction, sinusitis, nasal polyps and may be associated with allergic conjunctivitis, and atopic dermatitis. Allergic Rhinitis may also contribute to learning difficulties, sleep disorders, and fatigue.

Allergic rhinitis can frequently lead to significant impairment of quality of life. Symptoms such as fatigue, drowsiness (due to the disease or to medications) and malaise can lead to impaired work and school performance, missed school or work days, and traffic accidents. The overall cost (direct and indirect) of allergic rhinitis was recently estimated to be $5.3 billion per year.

Classification

Earlier allergic rhinitis was subdivided (based on time of exposure) as:

1. Seasonal
2. Perennial
3. Occupational

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Seasonal allergic rhinitis is related to outdoor allergens such as, pollens or moulds.[26] Perennial allergic rhinitis is caused by indoor allergens such as dust mites, moulds, insects and animal dander.[26] In November 2001, ARIA (Allergic Rhinitis and its impact on Asthma) panel in association with World Health Organisation proposed a new classification.

1. Persistent – More than 4 days per week or for a duration of more than 4 weeks
2. Intermittent - Less than 4 days per week or for less than four weeks duration

The symptoms are graded as:[13]

1. Mild – normal sleep, no impairment of daily activities, no troublesome symptoms
2. Moderate – abnormal sleep, slightly impaired daily activities, troublesome symptoms
3. Severe – impaired sleep, markedly impaired daily activities with severe symptoms

AETIOLOGY

The development of allergic rhinitis depends on:

1) Atopic state of sensitivity to an allergen
2) Exposure of sensitized subject to allergen

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Principle cause of allergic rhinitis is sensitivity to inhalant allergens.[27] Atopy refers to tendency to develop an exaggerated IgE antibody response as reflected by a positive skin prick test response to one or more common aero-allergens. Allergy represents the clinical expression of atopic disease. The common allergic disorders include rhinitis, asthma and eczema. Atopy is genetically inherited as confirmed by family studies. The mode of inheritances is autosomal dominant, recessive, mixed and multifactorial.[6]

Allergens

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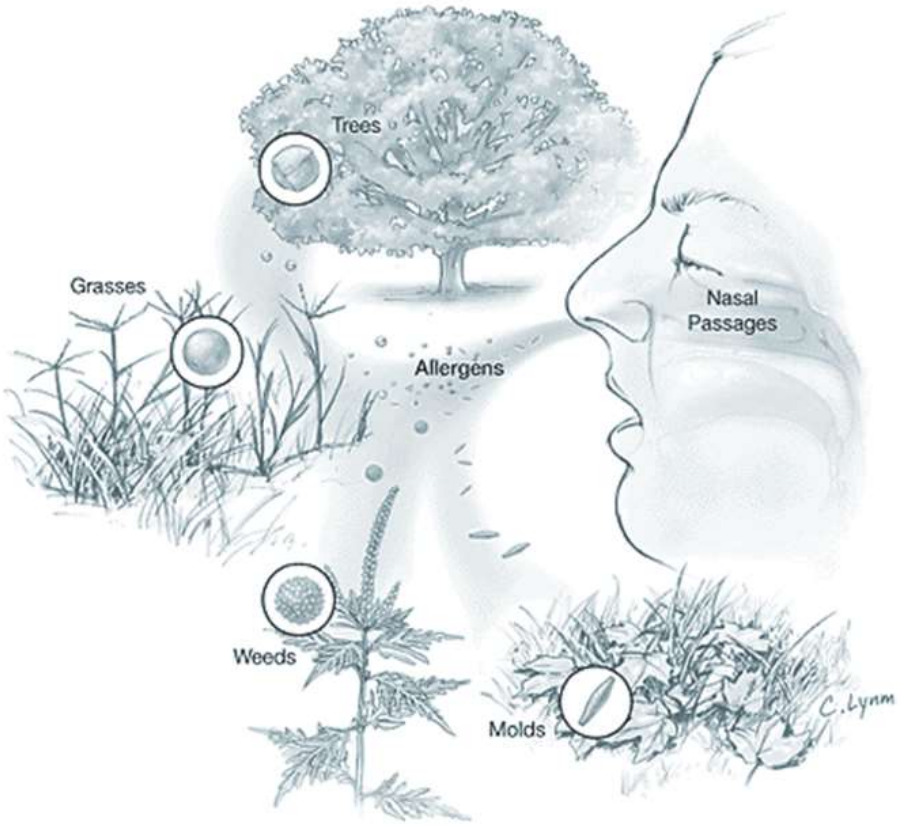

Figure 4: Various allergens

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1. House Dust

Dust of household origin is the most common known allergen and can cause both rhinitis and asthma. House dust is a complex mixture of animal dander, fungi, algae and insect debris, remnants of plant origin and food along with human epithelial scales.

2. Mites

"DERMATOPHAGOIDIS" is the most common allergen.

Most of the asthmatic population and patients of persistent allergic rhinitis are sensitized to mites that feed on human skin dander, which are abundant in mattresses, bed bases, pillows, carpets, upholstered furniture and fluffy toys. Their growth is maximal under hot (> 200 C) and humid conditions (80% of relative humidity) when humidity is <than 50%, mites dry out and die. House dust mite allergen is present in faecal pellets (10-20 µm).[28]

3. Pollens

Pollen grain is the male gametophyte of vegetable kingdom. Pollen allergens are found in grass, certain weeds such as compositeae family and tree pollens such as birch cuprussacea, mountain cedar, oak and olive tree. The size of pollen is about 10 to 1001µm. This is the reason why pollen depositions occur in nostrils and in eyes causing rhinitis and conjunctivitis.[29]

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4. Fungal allergens

Superior fungi, moulds and yeast are plants which do not possess chlorophyll but which liberate large quantities of allergic spores into atmosphere. **Moulds and yeasts** are known allergens in children to provoke rhinitis and asthma than in adults. Mould spore measure about (3 to 10 mm) that enter deep into the respiratory tract. Candida albicans, Saccaromyces and Pityrosporum are the most allergic yeasts.[13]

5. Insect and animal allergens

Insects belonging to the arachnida and hexapoda group have been implicated to cause allergy. Cats and dogs are main source of animal allergens. Major cat allergen (Fel d1) is a glycoprotein, which is transported in air by particles smaller than 2.5µm. These particles can remain air borne for prolonged periods. Major dog allergen (Can f 1) is a principally found in dogs fur and can also be found in saliva, skin and urine.[30]

Other causes include allergens from animal dander, food sources and occupation

Role of pollution:

Nasal hyper reactivity refers to a heightened sensitivity of the nasal mucosa to a range of non-specific irritants. Typical irritants include smoke, perfumes, tobacco smoke, traffic fumes, domestic sprays and bleach. Watery rhinorrhea following changes in temperature is also extremely common and almost diagnostic of the presence of nasal hyperreactivity.

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Irritants in high concentrations may provoke acute nasal symptoms in everyone, where as lower levels of exposure may provoke symptoms in patient with 'idiopathic' rhinitis and nasal hyper reactivity or in patient with nasal hyper reactivity associated with allergic rhinitis.

Exhaust fumes include nitrogen dioxide, ozone and diesel particulates. Diesel particulates have been shown to be adjuvant for antibody production in vivo in animals. Very recent data suggest that pre-exposure to a combination of nitrogen dioxide and ozone may amplify subsequent pollen – induced immediate symptoms of rhinitis.[15]

PATHOGENESIS

Allergic rhinitis is an immunologic process that involves the production of immunoglobulins in class of IgE. An antigen enters the nasal cavity and alights a permeable mucous membrane. It migrates into submucosal region, which is rich in vascular tissue and macrophages. The macrophage entraps the antigen and transports the exogenous material to T-lymphocytes that encode the antigenic material and stimulate the production of antibodies to the allergen in B-lymphocytes. B Lymphocytes then migrate to tissue and IgE, antigen specific, will be secreted into the interstitial tissues. After this, subsequently rechallenge by specific antigen causes binding of two IgE antibodies to the exogenous material that then lock onto a mast cell receptor site.

The mast cells are abundant in nasal tissue. The linkage of antigen and antibodies onto the mast cells stimulates degranulation and extrusion of granules into interstitial tissue. The chemical mediators, within the granules are released. These chemical mediators lead to symptoms and signs of allergic rhinitis. Histamine, present in the mast cells granule, when

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released, causes an immediate (within minutes) biochemical process that locally affects tissue, producing an increase in epithelial and endothelial permeability, plasma protein leakage hyper secretions, itching sneezing, nasal obstruction, rhinorrhoea and pruritus.[6]

A plethora of other substances such as, platelet-activating factor, eosinophilic chemotactic factor, arachidonic acid, kallikreins are released. These substances induce a biochemical cascade of reactions that lead to delayed responses (hours) that propagate inflammatory reaction. These reactions lead to symptoms of nasal inflammation, nasal obstruction, rhinorrhoea, pruritis, and sneezing.[6]

The allergic individual may be one who has an overproduction of specific IgE, one with a diminished T – lymphocyte suppressor system regulating IgE production, or a diminished suppressor system for the chemically mediated cascading response.[6]

To develop allergic rhinitis, a patient must have a special predilection for becoming immunologically sensitive to common environmental allergens. This atopic state tends to be familial and may manifest as eczema, rhinitis, or asthma, alone or in combination. Those destined to have rhinitis are not actually born allergic but have a capacity to become allergic. There is considerable evidence that a, primary exposure to an allergen is essential to developing sensitivity to it.

Atopic patients exposed to the same allergens do not necessarily develop the same patterns of sensitivity. Many patients with allergic rhinitis are clinically, and by skin test, sensitive to more than one inhalant, but the thresholds of reactivity vary considerably, with some reacting to very small allergenic challenges and others tolerating heavy doses of allergens before developing symptoms. The pattern and degree of sensitivity are often established in early

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childhood, once the allergen crosses the nasal mucosa, the atopic patient reacts in a distinctly different manner from the nonatopic patient. The lymphoid tissues produce an immunoglobulin capable of sensitizing membranes to subsequent challenge by allergens that are inhaled, ingested, or applied to the skin. The antibody, historically termed reagin but more recently labelled cytotropic, is present in serum in trace amounts and, as the term cytotropic suggests, it has a strong affinity for fixing to cells, particularly to the mast cells in the skin, intestines, nose, and bronchi. Immunochemically, the, antibody is identified and classified as IgE. Patients with allergic rhinitis have distinctly higher levels of specific IgE in the serum than do normal subjects. Artificial immunization experiments through the nose with tetanus toxoid produce higher levels of IgE in the nasal secretions in atopic patients than in nonatopic patients. Some IgE is produced by nonatopic patients, but high levels of IgE antibody sufficient to mediate allergic reactions are only found among atopic patients.

Studies on the regulation of lg E synthesis in humans show that T cells play a critical role in both mediating and enhancing suppressor signals to the Ig E producing B cells. In normal subjects the suppression overshadows enhancement, and in the atopic person the influence of the helper T cell exceeds that of the suppressor T cells on IgE synthesis. Although there is no specific therapy currently available to modulate the T cell effects in allergic patients, the present level of understanding of the system points toward the potential isolation of suppressor factors that might affect the regulation of IgE synthesis.

The allergic response in the nose is a product of an interaction between the IgE antibody and the allergenic molecule-'on the surface of the mast cell, resulting in the release of mediators from its granules. Histamine, slow-reacting substance of anaphylaxis and eosinophilic

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chemotactic factor are some of the mediators identified. The effect of these active pharmacologic agents in the nose produces capillary dilatation, increase mucous secretion, and attract eosinophils, basophils and leukocytes to the site of reaction.

In patients with seasonal allergic rhinitis, there is an almost immediate response to exposure to a few grains of pollen, a reaction that subsides within an hour after the challenge has been withdrawn. In about 60% of patients, however, symptoms recur 4 to 8 hours later. This reaction is called the late phase reaction (LPR). The study of the mediators, cells, and physiological responses of the LPR show there are both similarities with and differences from the immediate reaction that explain the patient's symptoms and response to therapy.

The immediate reaction is almost entirely a mediator-induced vascular response characterized by pruritus, capillary dilatation, and leakage. The late phase reaction is more cellular with additional mediator release. Eosinophils, basophils, and leukocytes create an inflammatory state in the tissues lasting 24 to 48 hours or longer if the allergic challenge continues to occur. The resulting congestion of the tissues of the nose disturbs the finely balanced autonomic nervous control of nasal function.[27]

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CLINICAL FEATURES

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Effective treatment of rhinitis symptoms depends upon accurate clinical diagnosis and assessment of patient's dominant symptoms. In general, the diagnosis of allergic rhinitis is straightforward and dependent upon clinical history.

Although allergic rhinitis can be caused by several different allergens, the clinical picture does not depend on type that cause the reaction because the same mediators are released whatever the allergen. A careful history, local examination of the nose and performance of skin prick tests should be performed in all patients presenting with rhinitis symptoms. Additional tests including flexible and rigid nasal endoscopy, mucociliary clearance studies and immunological tests may be required in certain circumstances. It should be remembered that the nose represents a 'window' to the respiratory tract and may also reflect systemic disease elsewhere.

Symptoms

The characteristic symptoms of allergic rhinitis are sneezing, watery rhinorrhoea, itching of nose and nasal obstruction. Symptoms of pruritus, nasal obstruction, sneezing and rhinorrhoea are thought to be due to sensory nerve stimulation, mucosal oedema and increased mucus secretions.[31] The symptoms occur within 5-15 min, of exposure to allergen and sneezing occurs in spasms of 10-20 at a time, which can exhaust the patient. Watery rhinorrhoea is usually very profuse. Very common complaint is annoying itching of nose and nasal obstruction, which is usually of moderate severity

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Signs

Physical examination should focus not only on nose, but examination of facial features, eyes, ears, oropharynx, neck, lungs and skin is also important. Look for physical findings that may be consistent with a systemic disease that is associated with rhinitis.

Nose

"Nasal crease" is a horizontal crease across lower half of bridge of nose that is caused by repeated upwards rubbing of tip of nose by palm and hand (i.e., allergic salute). The mucosa of nasal turbinates may lead to swollen (boggy), pale turbinates. Thin and watery secretions are frequently associated with allergic rhinitis, while thick and purulent secretions are usually associated with sinusitis, however, thickness, purulent, coloured mucus can also occur with allergic rhinitis. Examine nasal cavity for polyps, deviated nasal septum.

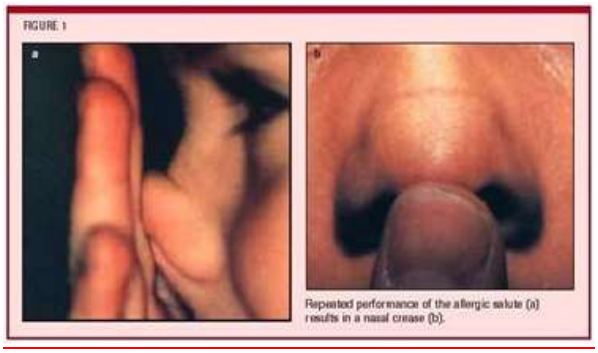

Figure 5: Allergic salute and transverse crease

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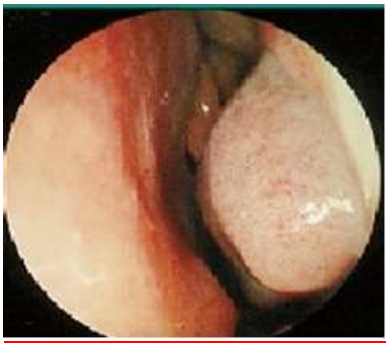

Figure 6: Endoscopic veiw of nasal mucosa in allergic rhinitis

Ears, eyes and oropharynx

Tympanic membrane retraction, air fluid level or bubbles in tympanic cavity and restricted tympanic membrane mobility can be associated with a allergic rhinitis, particularly if Eustachian tube dysfunction or secondary otitis media is present.

Ocular examinations may reveal findings swelling of palpable conjunctiva with excess tear production. Dennie – Morgan lines (prominent creases below the inferior eyelid) are associated with allergic rhinitis.

Term “cobble stoning” is used to describe streaks of lymphoid tissue on posterior pharynx, which is commonly observed in allergic rhinitis.

Neck - look for evidence of lymphadenopathy or thyroid disease. Lungs - look for characteristic findings of asthma. Skin – evaluate for possible atopic dermatitis.[32]

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Seasonal rhinitis:

The first symptom of the hay fever season is usually sneezing. In severe cases paroxysms of sneezing occur at frequent intervals throughout the day. Sneezing is probably largely due to histamine release acting through reflexes. Excessive fluid and mucus secretion (rhinorrhea) is believed to be the response of serous and seromucous glands to mast cells/basophil derived mediators. Nasal obstruction or blockage is the result of vascular engorgement, which is due to vasodilatation and oedema. Itchiness of nose, eyes, palate are common features. Tearing, itching and tenderness of the eyes together with some degree of periorbital oedema is usual in hay fever. Other symptoms include tightness of the chest (sometimes with wheezing) and a burning or raw sensation in the throat.

Perennial rhinitis:

The symptoms of perennial rhinitis differ slightly from seasonal rhinitis largely as a result of long-standing nasal mucosal inflammation in the treated situation. Sneeze, itchiness and nasal discharge are prominent, but the rhinorrhea may be more viscous or purulent depending on the degree of cellular recruitment. Conjunctivitis is far less frequent in perennial than in seasonal rhinitis. It is also accompanied by varying degrees of loss of smell (anosmia), loss of taste (ageusia) and symptoms associated with the Eustachian tube (hearing defects and ear pain).[33] A number of typical stigmata occur, particularly in allergic children. Frequent nose rubbing "the

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allergic salute" which is characterized as follows; the hand lifts the nasal tip to respond to itching while temporarily opening the airway, a transverse nasal crease appears caused by repetition of this manouvre and facial grimacing and twitching are present due to itching membranes and a bluish-black discoloration under the lower eye lid (allergic shiners).[3]

Differential diagnosis

Vasomotor rhinitis, gustatory rhinitis (vagally mediated), rhinitis medicamentosa, hormonal rhinitis (related to pregnancy, hypothyroidism, oral contraceptive use) Anatomic rhinitis (Eg – Deviated nasal septum, Choanal atresia, adenoid hypertrophy, foreign body),immobile cilia syndrome (ciliary dyskinesis), cerebrospinal fluid leak, nasal polypi, granulomatous rhinitis (eg. Wegener's granulomatosis, sarcoidosis).[34]

Laboratory tests

Allergy testing

Testing for reaction to specific allergens can be helpful to confirm diagnosis of allergic rhinitis and to determine specific allergic triggers.

A. Invivo test

Allergy skin test (immediate hypersensitivity testing) is an in vivo method of determining immediate (IgE – mediated) hypersensitivity to specific allergens. By introducing an extract of a suspected allergen percutaneously, an immediate (early phase) wheal and flare reaction can be produced

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1. **Skin prick test**

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Percutaneous introduction can be accomplished by placing a drop of extract on skin and scratching or pricking a needle through the epidermis under the drop. The size of wheal and flare reaction roughly correlates with degree of sensitivity to allergen. The allergen can also be introduced intradermally. Skin prick tests are preferred to scratch or intradermal tests, which are less reproducible, more dangerous and may give false – positive responses. Skin prick testing is inexpensive, accurate rapid and can be undertaken with a wide variety of allergens at a single skin prick testing session.

In vitro allergy tests, radioallergosorbent test allows measurement of amount of specific IgE to individual radio isotope labeled allergens in a sample of blood. The amount of specific IgE produced to a particular allergen approximately correlates with allergic sensitivity to that substance. The sensitivity and specificity are not always as good as accurate skin testing.

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Figure 7: Skin prick test kit

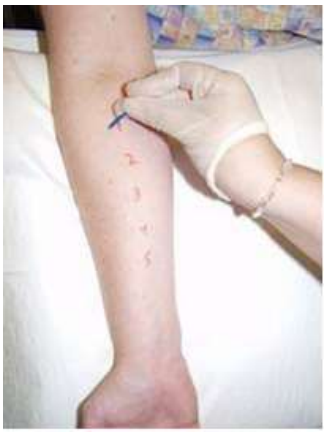

Figure 8: Skin prick Test

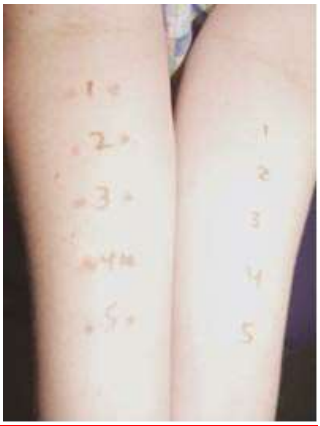

Figure 9: Positive test

2. **Total serum IgE**

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This is measurement of total level of IgE in blood. While patients with allergic rhinitis are more likely to have an elevated total IgE level than normal population, this test is neither sensitive nor specific for allergic rhinitis.

3. **Total blood eosinophil count**

As with total serum IgE, an elevated eosinophil count supports the diagnosis of allergic rhinitis, but it is neither sensitive nor specific for diagnosis.

4. **Nasal smear cytology**

It is helpful in differential diagnosis of nasal complaints. Samples may be obtained either by blown secretions or by gentle scrapping of lateral nasal wall. Material is smeared on to glass slide fixed in ethanol and stained with May Grunwald or Giemsa. Presence of eosinophils, neutrophils, basophils, mast cells, epithelial cells and bacteria should be recorded. If there are more than 15% eosinophils it indicates allergy. Increased neutrophils and epithelial cells indicates infection. Increased mast cell shows nasal mastocytosis.[35]

5. **Nasal provocation test**

Crude method to challenge nasal mucosa with small amount of allergen placed at end of tooth pick and patient is instructed to sniff into each nostril. Observe if allergic symptoms are reproduced. But, test is time consuming and technically demanding because it requires one agent to be tested at a time.[13] It can also precipitate anaphylaxis/bronchospasm.

COMPLICATIONS:

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It has been suggested that allergy may contribute to serous otitis media. However, the evidence is conflicting: some studies have not demonstrated a greater prevalence of atopy and allergy in otitis media patients compared with normal control subjects. It is possible that pathological changes associated with rhinitis may lead to obstruction of the eustachian tube with dysfunction and middle ear effusion. It seems more likely that serous otitis is not allergic disease per se but a frequent complication of nasal allergy, particularly in children. The association between allergy and sinusitis is essentially twofold. First, allergy may contribute to obstruction of the sinus ostia. Second, perennial allergic rhinitis has some of the features of chronic sinusitis particularly nasal discharge and obstruction Allergic rhinitis may sometimes be associated with bilateral ethmoid polypi, but is more common with eosinophilic non-allergic rhinitis. Allergic rhinitis and bronchial asthma frequently coexist. It is important to recognize and treat associated asthma. Furthermore, treatment of rhinitis with improvement in the nasal airway may also improve symptoms of bronchial asthma.[2]

Management

The mainstay of treatment of allergic rhinitis involves identification and avoidance of provoking allergens (wherever possible) and use of topical corticosteroid nasal spray and oral antihistamines. Immunotherapy retains a place in treatment of patients with severe isolated grass pollen allergy. Surgery should not be considered "a last resort" but rather complementary to medical treatment of allergic rhinitis, when this is complicated by structural problems such as deviated septum, nasal polypi and enlarged turbinates.[6]

1. Allergen avoidance[36]

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Management of patients with rhinitis symptoms should always include identification and where possible avoidance of causal factors. The nature of offending agent usually can be obtained from patient's history or through testing. In house dust sensitive patient, changing the filters on the furnace, removing dust catching surfaces and frequent cleaning may be of great benefit. Slight dampening of lawn prior to moving will cut down the amount of dust and diminish density of mold spores that would be placed into the environment while moving the lawn. During summer months, air conditioning has been found to be an effective filtration of dust and pollen materials. Allergic patients should be encouraged not to sleep with window open it is necessary for practitioner to become aware of environmental and occupational surroundings of the individual.

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2. Pharmacotherapy

Antihistamines

Antihistamines were the first effective drugs to be used for symptomatic relief of allergic diseases. They are competitive blockers of histamine at H1 receptor. These block the local effect of released histamine from mast cells or basophils. By interfering with this phase, they attenuate inflammatory response mediated by histamine.

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Three receptors exist for histamine. H1 receptors are found on blood vessels, on sensory nerves, on smooth muscles of the respiratory and digestive tracts, and in the central nervous system. Stimulation leads to vasodilatation, increased vascular permeability, sneezing, pruritus,

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glandular secretion, and increased intestinal motility. H2 receptors have a distribution similar to that of H1 receptors but are principally involved in the regulation of gastric acid secretion. H3 receptors are located principally in the brain and seem to be involved in the regulation of histamine synthesis and release. The contribution of histamine to the early allergic response, largely mediated by the H1 receptor, has long been recognized and is the rationale for the large number of H1 antagonists in clinical use. The first generation of antihistamines are effective, but they have some undesirable side effects because of their lipid solubility, lack of selectivity and subsequent nonspecific stimulation of other receptors. Among these side effects are sedation, anticholinergic effects, functional and performance impairment, and gastrointestinal distress. Eg: Chlorpheniramine, brompheniramine, triprolidine and diphenhydramine

Second – generation antihistamines are less lipophilic than first generation H1 antihistamines and do not penetrate the blood brain barrier. Their greater receptor selectivity also reduces the incidence of anticholinergic side effects. Treatment with some antihistamines also reduces the production of leukotrienes and kinins, which are mediators with proinflamamtory effects, as well as the allergen induced increased responsiveness to methacholine. Another anti-inflammatory property of antihistamines is a reduction of soluble ICAM-1 levels in nasal secretions, a property demonstrated by both loratidine and cetirizine. Oral antihistamines are readily absorbed. Their onset of action is rapid, usually within 60 minutes, and maximum benefit occurs within hours. Metabolism of most antihistamines occurs primarily through the hepatic cytochrome P-450 system. One exception is cetrizine, which is primarily excreted in the urine and does not depend on the cytochrome P-450 system. The clinical effectiveness of antihistamines exceeds the duration of measurable serum levels. This phenomenon may be attributable to the presence of active metabolites.[17]

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A newer generation of antihistamines includes those that are used topically (eg: livastin, azelastine) and 'designer' antihistamines that are metabolites and congeners of existing drugs (eg: fexofenidine, desloratadine, levocetirizine, etc) with fewer potential side effects but increased effectiveness.[3] Azelastine, a phthalazinone derivative is an intranasal preparation with efficacy comparable to that of other antihistamines. Although it does not cause somnolence, azelastine may cause a sensation of altered taste immediately after use.[17]

Corticosteroids

Intranasal corticosteroids are very helpful in treatment of allergic rhinitis. Primary mode of action is in the phase of inhibition of conversion of arachidonic acid to leukotriene and prostaglandin pathways. Corticosteroids also have other effects including vasoconstriction and antipyretic effect. They inhibit leukocyte mobilization and depress antibody formation. One half of all nasally administered steroids may be absorbed from nasal mucosa. A portion of material is also swallowed and absorbed from gastrointestinal tract. However with exception of Dexamethasone, all nasal steroids undergo extensive first pass hepatic metabolism to either inactive or less active compounds. This metabolism along with pharmacodynamics of individual preparation prevents significant systemic side effects unless administered at higher than recommended doses.[8]

Hydrocortisone is the parent molecule from which the natural and synthetic anti-inflammatory steroids are derived. The lipophilic nature of steroids permits rapid absorption across mucosal surfaces.[4] These agents profoundly reduce multiple aspects of the inflammatory response to allergen.

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Corticosteroids penetrate the interior of the cell; where they are bound by a glucocorticoid receptor in the cytoplasm. The glucocorticoid-receptor complex then penetrates the nucleus, where it inhibits the synthesis of the proinflammatory cytokines IL-1, -2, -3, -5 and –6; interferon-γ; tumor necrosis factor-α and GM-CSF and induce the synthesis of other anti-inflamamtory substances such as vasocortin and lipocortin. These agents reduce eosinophil survival and function induced by IL-1, -3 and –5.

Treatment with intranasal corticosteroids also reduced the antigen induced hyper responsiveness of the nasal mucosa to the subsequent antigen and histamine provocation. Intranasal corticosteroid administration also leads to a reduction in inflammatory cells and TH2-type cytokines within the nasal mucosa. In addition, they increase the level of TH1-type cytokines such as interferon-γ and IL-12, which can suppress the transcription of IL-4.[17]

Currently, nasal corticosteroids are administered as either a pump spray (generally in an aqueous vehicle) or as a suspension dispensed in a powerful fashion by a propellent. All topical nasal corticosteroids may cause side effects such as local nasal irritation, crusting, epistaxis or even nasal septal perforation.[3] Various preparations available include beclomethasone, flunisolide, budesonide, triamcinolone, dexamethasone, fluticasone and mometasone. It seems wise to use the newer agents with the lower systemic bioavailability such as mometasone and fluticasone. These agents have been approved by the US food and Drug administration (FDA). Mometasone and fluticasone are poorly absorbed from the gastrointestinal tract, with the remaining fraction of absorbed drug rapidly metabolized by the liver.[17]

Decongestant

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Decongestants exert their effect through stimulation of α1 adrenergic receptors. These receptors are present on resistance vessels, where they control blood flow, and on capacitance vessels, where they control blood volume. They produce vasoconstriction in turbinates, decreasing nasal congestion. When topically applied for more than 5-7 days, it may produce rebound rhinitis. Common orally administered decongestants are pseudoephedrine, phenyl propanalamine and phenylephrine. Oral decongestants exert their effects directly and by stimulating norepinephrine release. Because oral decongestants also stimulate adrenergic receptors other than those in the nasal vasculature, over dosage has been associated with hypertensive crisis. Their major side effect is insomnia, which occurs in approximately 25% of patients.

Topical decongestants are effective in reducing nasal congestion, regardless of the cause, and these include catecholamines (such as phenylephrine) and imidazoline derivatives (such as xylometazoline or oxymetazoline). Prolonged use can bring about rhinitis medicamentosa, which is characterized by rebound nasal congestion after cessation of therapy. Because this phenomenon can appear even after a short period, use of these agents should be limited to a few days.[17]

Potential side effects of these drugs are related to their vasopressors actions, which may cause elevated blood pressure in patients with pre-existing hypertension and central nervous system stimulation in patients taking tricyclic antidepressant or monoamine oxidase inhibitors. They are often combined with first or second-generation antihistamines.[8]

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Mast cell stabilizers

Sodium cromoglycate inhibits secretion of granules in mast cells and basophils. Cromoglycate exerts a protective effect on the allergic response before the development of symptoms. Although it was initially thought to prevent mast cell degranulation, the exact mechanism of action of this agent is unknown. It does not inhibit binding of IgE and specific antigen. It is prophylactic treatment of allergy, most beneficial when used prior to an anticipated allergen exposure, but must be administered atleast 4 times daily for maximum effect.[37] It is well tolerated and has no side effects except for local irritation. Newer drug in class of mast cell stabilizers is nedocromil sodium, is considered to be more effective than sodium cromoglycate.[8] Like antihistamines, cromolyn is more helpful for sneezing, rhinorrhea and nasal itching than for nasal congestion. Its safety profile, however, makes it an attractive treatment, especially in children and pregnant women. The potency of this agent parallels that of antihistamines but is less than that of intranasal corticosteroids.[17]

Anti-cholinergics

Iprotropium bromide is locally acting, mainly helps patients with watery rhinorrhoea. It has no effects on other symptoms.[8] Anticholinergic agents inhibit parasympathetic stimulation of glandular secretion by competing for muscarinic receptors on glands. The dosage should be titrated to avoid excessive drying of the nasal mucosa and epistaxis, which are the most frequent side effects. This agent serves as a useful adjuvant therapy with topical corticosteroids and antihistamines for control of rhinorrhea.[17]

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Leukotriene modifiers:

Among the numerous mediators released into the nose on antigen challenge, leukotrienes have been shown to contribute to nasal congestion in allergic rhinitis. Symptoms of allergic rhinitis have been shown to be reduced by two clinically available leukotriene modifiers, zafirlukast and montelukast. The combination of a leukotriene modifier with an antihistaminic increases the efficacy of both medications. This combination can be considered as an alternative in patients who do not tolerate intranasal corticosteroids.[17]

Immunotherapy

It is a process in which increased doses of allergen are subcutaneously injected over time, as a treatment to prevent allergic symptoms that occur on exposure of allergen. It has been used widely since early 1900's. Important mechanism of action is changes in relative activity of T-lymphocytes helper and suppressor cells with decrease in allergen specific IgE antibodies. It also prevents rise in chemotactic factors. Intradermal injections are administered in increasing concentration once or twice weekly until effects are noted and then maintenance dose given for a period of one year once a month. It is discontinued if uninterrupted treatment for 3 years shows no clinical improvement.[6] To overcome the drawback of length of time in conventional immunotherapy, rush immunotherapy has been attempted where increased dose is given and maintenance dose achieved by 2 to 5 days, thus decreasing time consumption.[13] Immunotherapy should be considered in pollen sensitive patients who fail to respond to conventional treatment. Allergen immunotherapy represents a specific treatment for allergic disease and, unlike conventional pharmacological treatment has at least the theoretical potential to alter the course of allergic disease with, for example, prevention of progression of allergic rhinitis to asthma.[2]

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1. FLUTICASONE FUROATE[38]

Introduction:

Fluticasone furoate (FF) is a new topical intranasal corticosteroid, with enhanced affinity and an unique side-actuated delivery device. It has shown good efficacy in improving nasal and also ocular symptoms of AR in all age groups (>2 years). A prolonged nasal retention time allows for a once-daily dosing regimen which would improve compliance. It has acceptable odour, aftertaste, mist gentleness and minimal leaking out of the nose and down the throat with less systemic adverse effects including minimal HPA axis suppression in children.[39,40]

Structure:

IUPAC name: (6α, 11β, 16α, 17α)-6, 9-difluoro-17-{[(fluoro-methyl) thio] carbonyl}-11-hydroxy-16-methyl-3-oxoandrosta-1, 4-dien-17-yl 2-furancarboxylate

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Figure 10: structure of fluticasone furoate

Mechanism of action

The precise mechanism through which FF reduces rhinitis symptoms is not known. Corticosteroids have a wide range of actions on multiple cell types (e.g., mast cells, eosinophils, neutrophils, macrophages, lymphocytes) and mediators (e.g., histamine, eicosanoids, leukotrienes, cytokines) involved in inflammation. Specific actions of FF seen in experimental sensitized rats were activation of the glucocorticoid response element, inhibition of pro-inflammatory transcription factors such as Nuclear Factor kappa-B (NFkB), and inhibition of antigen-induced lung eosinophilia.

FF is a synthetic trifluorinated corticosteroid with potent anti-inflammatory activity. It has a molecular weight of 538.6. FF nasal spray is an aqueous suspension of micronized FF for topical administration by means of a metering atomizing spray pump. Each actuation delivers 27.5 µg of drug in a volume of 50 µl suspension that also contains 0.015% w/w benzalkonium chloride, dextrose anhydrous, edetate disodium, microcrystalline cellulose, carboxymethylcellulose sodium, polysorbate 80, and purified water. It is supplied commercially in a 10-g bottle

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containing 120 sprays. The availability of the drug in a side-actuated device makes medication delivery simple and consistent, thus improving patient compliance.

Fluticasone furonate has high receptor affinity, with low equilibrium dissociation constant (kd 0.3 nmol/L) and with greater relative receptor affinity (2989) than mometasone furoate (2244), fluticasone propionate (1775), beclomethasone-17- monopropionate (1345), ciclesonide active principle (1212), and budesonide (855). Some in vitro studies shows that FF displayed greater potency than other corticosteroids in inhibiting tumor necrosis factor synthesis and its action. It was also more potent in preventing damage to cultured human lung epithelial cells by different stimulus. Experimental studies demonstrated more potent and faster anti-inflammatory activity of FF than fluticasone propionate.[41] FF displayed high selectivity for the glucocorticoid receptor in vitro and had no effect on the hypothalamopituitary- adrenal (HPA) axis in children or adults during clinical trials.[42,43]

Pharmacokinetics

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The onset of action of FF nasal spray is rapid and is observed 8 h after the first dose of medication. It has been developed for the treatment of AR in patients 2 years of age and older and is administered via a unique, side-actuated device. FF is administered once daily and its recommended starting dose is 55 µg for children and 110 µg for adults and adolescents. It has greater affinity for the glucocorticoid receptor when used intranasally and demonstrates prolonged receptor binding properties resulting in prolonged action and 24-h coverage with single daily dosing. Systemic bioavailability is the sum of the drug that is absorbed via the nasal mucosa plus that is swallowed (approximately 40-90% of the drug administered). Following intranasal administration, most of the swallowed dose undergoes incomplete

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absorption and extensive first-pass by the hepatic isoenzyme, CYP3A4, resulting in negligible systemic exposure (oral bioavailability is <0.5%). Since FF undergoes extensive first-pass metabolism in the liver, the pharmacokinetics of FF may be altered in patients with hepatic impairment and hence caution is recommended in them. It falls in Pregnancy Category C.

Intranasal FF 880 µg when administered every 8 hourly for 10 doses in healthy adult volunteers showed the average absolute bioavailability was 0.5%. Oral bioavailability after 2 mg single oral dose is 1.26% and elimination half-life after single intravenous dose is 15.1 hours.[39] FF is 99.4% bound to plasma protein in vitro indicating extensive first-pass metabolism of the absorbed drug.[41,44] Protein binding is highly relevant because only the unbound free drug can exert an effect at the receptor site. As long as the corticosteroid is bound to a protein, it is unable to bind to its receptor. Clearance of FF is primarily by hydrolysis in the liver by the cytochrome P450 isozyme (CYP) 3A4 that converts the drug to the 17[beta]-carboxylic acid metabolite (M10), which displays low glucocorticoid receptor agonist potency. The drug is excreted mainly in the feces, with only minor amounts in the urine.[39,45] FF is a synthetic, lipophilic, corticosteroid.[46] Agents highly lipophilic will demonstrate a higher and faster rate of uptake by the nasal mucous membrane, a higher level of retention within the nasal tissue, and an enhanced ability to reach the glucocorticoid receptor.

Dose:[39]

Children 2 to 11 years of age

The recommended starting dosage in children is 55 mcg once daily administered as one spray (27.5 mcg/spray) in each nostril. It may be increased to 110 mcg (two sprays in each nostril) once daily in non responders.

Adults and adolescents 12 years of age and older

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The recommended starting dosage is 110 mcg once daily administered as two sprays (27.5 µg/spray) in each nostril. When the maximum benefit has been achieved reducing the dosage to 55 mcg (one spray in each nostril) once daily may be effective in controlling symptoms of allergic Rhinitis.

Indication[38]

FF nasal spray is indicated for seasonal and perennial allergic rhinitis in patients aged two years and older. It has shown to consistently reduce ocular symptoms of SAR.

Drug interactions[38]

FF is cleared by extensive first-pass metabolism in the liver; hence potent inhibitors of CYP3A4 enzyme may increase exposure to FF thereby increasing the risk of adverse effects. Caution is recommended when used with ketoconazole, ritonavir and other hepatotoxic drugs.

Clinical efficacy[38]

FF has been compared with placebo in various Randomized Control Trials (RCTs) in adults and children. FF nasal spray was observed to produce significantly greater improvements than placebo in relieving nasal, ocular and night time symptoms of both SAR and PAR.

Adverse effects[39,47]

Occurrence of systemic side-effects is limited by the targeted delivery of the medication to nasal mucosal. The low potential for causing systemic side-effects has been established in both short- and long-term studies. The most common adverse drug reactions are headache, epistaxis, nasopharyngitis, pyrexia, pharyngolaryngeal pain, nasal ulceration, cough, back pain, impaired wound healing, immunosuppression and candida infections (prolonged usage)

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2. Azelastine hydrochloride[48]

Introduction:

Azelastine is a potent, second-generation, selective, histamine -H_1-receptor antagonist.[49] The chemical nomenclature of azelastine is (±)-1-(2H)-phthalazinone, 4-[(4-chlorophenyl) methyl]-2-(hexahydro-1-methyl-1H-azepin-4-yl)-monohydrochloride. It is white, almost odorless with a bitter taste. Azelastine has been formulated both as a nasal spray (0.1% and 0.15% solutions) and as eye drops (0.05% solution).

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Structure:

IUPAC name: (*RS*)-4-[(4-chlorophenyl) methyl]-2- (1-methylazepan-4-yl)-phthalazin-1-one

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Figure 11: Structure of azelastine hydrochloride

Mechanism of action:[50,51]

Azelastine has a triple mode of action

1. Anti-histamine effect,
2. Mast-cell stabilizing effect and
3. Anti-inflammatory effect.

Azelastine Hydrochloride, a phthalazinone derivative, and its major metabolite, desmethylazelastine exhibits histamine (H_1) receptor antagonist activity. In addition to this, it also has anti inflammatory and mast cell stabilizing properties. Azelastine has a rapid onset of action; 15 minutes with the nasal spray and 3 minutes with the eye drops. The effect lasts for 12 hours.[52]

Pharmacokinetics and metabolism

The bioavailability of azelastine is approximately 40% when administered intranasally. Maximum plasma concentrations (Cmax) are observed within 2–3 hours. The elimination half life, volume of distribution and plasma clearance are 22 h, 14.5 l/kg and 0.5 l/h/kg respectively when administered by intravenous and oral route.. It is oxidatively metabolized by

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the cytochrome P450 family into its active metabolite, desmethylazelastine, and two inactive carboxylic acid metabolites. Approximately 75% of oral dose is excreted in feces.

Dosage[52,53]

Azelastine nasal spray offers both flexibility of dose and dosage. For adults and children ≥ 12 years the recommend dosage is 1 or 2 sprays/nostril twice daily. For children aged between 5 and 11 years 1 spray/nostril twice daily is the recommended dosage. Because it has quick onsetit is used as and when symptoms arise. On-demand use of azelastine nasal spray results in acceptable clinical control of rhinitis symptoms, although it does not significantly reduce allergic inflammation as observed at fixed doses of 0.28 and 0.56 mg/day.

Indications:[54-56]

Azelastine nasal spray is indicated for treatment of the symptoms of seasonal allergic rhinitis and perennial allergic rhinitis, such as rhinorrhea, sneezing and nasal pruritus in adults and children 5 years of age and older. In some countries, it is also indicated for the treatment of vasomotor rhinitis in adults and children ≥ 12 years old. Eye drops are indicated for seasonal and perennial allergic conjunctivitis.

Safety and tolerability[57,58]

Azelastine is safe and well tolerated in both adults and children (≥12 years) with allergic rhinitis. Bitter taste, headache, nasal burning and somnolence are the most frequently reported adverse events. Certain prescribing recommendations warn against the concurrent use of alcohol and/or other central nervous system depressants, but to date there have been no studies to assess the effects of azelastine nasal spray on the CNS in humans. More recent studies have shown similar degrees of somnolence (approx. 2%) compared with placebo treatment. The problem of

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bitter taste may be reduced by correct application of the nasal spray (i.e. slightly tipping the head forward and not inhaling the medication too deeply), or alternatively using the azelastine /sucralose formulation. Other side effects include Dysgeusia, epistaxis, headache, nasal discomfort and fatigue

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DISCUSSION

Allergic rhinitis is a common chronic immunological disease.[1] The complications associated with it affect all the age groups with more predilection until the third decade of life. Even today despite advances in understanding of the numerous chemical mediators of allergy, only two major categories of drugs are used for the management, namely antihistaminics and corticosteroids.[3] The first line pharmacological treatment of allergic rhinitis has been a matter of discussion from several years.

One hundred and fifty patients were recruited for the study (figure 12). The mean age was 26.23 ± 5.21 and 26.96 ± 4.82 years in fluticasone furoate and azelastine hydrochloride group respectively, which is similar (28-32yrs) to other studies.[63,64] The probable reason could be the lifestyle activity which increases their exposure to a wide variety of allergens compared to older age group. Gender distribution was 50.6% males and 49.4% females (table 5) which was similar to earlier studies (38-62%).[65,66] Most of the patients presented with the three main symptoms of allergic rhinitis i.e. sneezing, nasal obstruction and rhinorrhea. Baseline demographic profile and parameters were comparable between the groups (table 6, 7). Around 50% of patients in our study had previous history of allergic rhinitis (figure 13) and the symptoms of allergic rhinitis aggravated during winter and in presence of dust and smoke (table 6).

In our study fluticasone furoate when administered intranasally significantly decreased all the parameters of total nasal symptom score and the Lund-kennedy endoscopic staging score (table 8, 9) ($p = 0.001$) by day 7 when compared to baseline in all the patients and by day 15 patients were symptom free. It also significantly improved the patient's satisfaction towards treatment (table 11) ($p = 0.001$) by day 7 as assessed by rhinoconjunctivitis quality of life questionnaire (RQLQ) which denotes improvement in quality of life. It also significantly reduced the ocular manifestations of allergic rhinitis which is one of the parameter of RQLQ.

A study demonstrated that, patients treated with Fluticasone nasal spray had greater reduction in total symptom score when compared with placebo ($p < 0.001$).[67,68] In other studies significant reduction was seen in nasal obstruction, itching and rhinorrhoea in fluticasone treated group compared with placebo and improvement in quality of life.[68] Studies have shown that fluticasone furoate reduces ocular manifestations in allergic rhinitis. Ocular symptoms of allergy can be particularly troublesome for the patient and are often difficult to treat. Fluticasone furoate was superior to placebo for reduction in ocular manifestations in patients suffering from allergic rhinitis. Possible mechanisms include reduced nasal inflammation resulting in decreased release of inflammatory mediators in the neighbouring tissues, improved drainage from the eye through the naso lacrimal duct.[69-71]

In the present study intranasal azelatine hydrochloride significantly decreased all the parameters of total nasal symptom score and the Lund-kennedy endoscopic staging score (table 8, 9) ($p = 0.001$) by day 7 when compared to baseline. The scores of the various parameters reduced to zero by day 15. It also significantly improved the patient s satisfaction towards treatment (table 11) ($p = 0.001$) by day 7 which denotes improvement in patient's quality of life.

Other studies have shown that azelastine therapy, improved total nasal symptom scores significantly than placebo.[72,73] It also improved sleep, reduced daytime somnolence and nasal congestion compared to placebo which was statistically significant.[53,54] In previous studies it was found that on treatment with antihistaminics, 80-90% patients had significant symptom relief, improved nasal air flow and reduced mean total nasal symptom score when compared to baseline at the end of two weeks ($p<0.001$). In an open-label trial patients receiving azelastine nasal spray for 2 weeks, majority of the patients reported some or complete control of post-nasal drip and sneezing. Improvement in sleep difficulties or impaired daytime activities was seen in 85% of the patients.[48] Azelastine showed a statistically significant improvement in the total nasal symptom score at 15 minutes compared with placebo, cetrizine and loratidine.[74,75]

When between the group analysis was done we observed that fluticasone furoate decreased the total nasal symptom and Lund-kennedy endoscopic score significantly compared to azelastine hydrochloride ($p = 0.001$) by day 7 (table 8, 9). Rhinoconjunctivitis quality of life questionnaire (RQLQ) score was significantly decreased by fluticasone furoate when compared to azelastine hydrochloride at the end of day 7 ($p=0.001$) which denotes improvement in quality of life (table 11).

When three different topical preparations of corticosteroids were compared with four different preparations of antihistaminics, topical nasal corticosteroids significantly improved sleep, sneezing, ocular and nasal pruritus, and nasal congestion than antihistaminics.[76] Another study reported improvement in symptom with fluticasone compared to loratidine ($p = 0.001$).[77] Similar results were found in other studies which concluded that intra nasal corticosteroids were better than H1 receptor antagonists and allergic rhinitis being an inflammatory disease is best managed with anti- inflammatory medications.[63,77] In a 6-week, placebo-controlled study, once-daily dose of 256 μg of budesonide nasal spray was ($P < 0.01$) more effective than azelastine.[48]

In this study the drugs reduced the absolute eosinophil count both in blood as well as nasal smears by day 15 compared to baseline which was statistically significant (table 10) ($p = 0.001$). We also observed that fluticasone furoate produced a significant ($p = 0.001$) reduction in both these parameters compared with azelastine hydrochloride. Absolute eosinophil count in the nasal smears ranged between zero to one in both the groups by day 15, but the number of patients who had a count of zero was more with fluticasone furoate (56) than azelastine hydrochloride (30).

The assessment of sensory attributes in patients receiving these drugs showed that the scores reduced significantly by day 7 (i.e the patient tolerated the drug well in both the groups), but it was significantly ($p=0.001$) better with fluticasone furoate when compared with azelastine hydrochloride (table 12). Patient preference in regard to specific sensory attributes of a drug may determine adherence to therapy.[78-82] Important sensory attributes include minimal odour, irritant effect, absent taste and product moistness. It has been shown that the intensity of

such sensory components is inversely correlated with preference. Sensory attributes vary considerably between current market preparations.[78-82]

In our study (figure 14) the adverse effects noted with fluticasone furoate were nasal stuffiness (33.33%) and irritation of nasal mucosa (12%). Studies have shown adverse effects like mild mucosal irritation and epistaxis.[63] In a pooled analysis of clinical trials, the overall incidence of adverse effects with intranasal fluticasone furoate was similar to placebo.[38] In another study when fluticasone furoate was used for atopic rhinitis for a duration of 12 months, it was well tolerated but occurrence of epistaxis was 20% compared to placebo (8%).[39] Studies suggest that usual doses of intranasal corticosteroids when given for duration of 2-12 weeks do not cause growth suppression in majority of patients.[83] Fluticasone furoate nasal spray 110 μg once daily for two weeks in a randomized, double-blind, placebo-controlled, crossover study was observed to have no effect on lower-leg growth rate in pre-pubertal children.[84]

The adverse effects seen (figure 15) with azelastine hydrochloride were nasal stuffiness (28%) and nasal irritation (8%). Other studies have reported bitter taste and sedation as adverse effects.[76] All the adverse effects noted in our study were mild to moderate. Patients in both the groups required only one metered dose nasal spray of fluticasone furoate or azelastine hydrochloride. The cost incurred with fluticasone furoate was 235.75 rupees per patient whereas for azelastine hydrochloride it was 187.25 rupees.

The advantages of topical over systemic drug admistration are that the medication can be delivered directly to the site of allergic inflammation, higher concentration of the drug can be achieved in nasal mucosa which wil enhance anti allergic and anti inflammatory effects of these drugs. A study has shown that 0.28 mg of azelastine administered intranasally has a faster onset of action than 2.2 mg administrated orally.[85] Topical application reduces the risk of interaction with concomitant medication and potential systemic effects.

Conclusion

- Allergic rhinitis is a chronic immunological disease caused by an IgE-mediated immune or immediate hypersensitivity mechanism, associated with sneezing, rhinorrhea and nasal obstruction.
- The treatment of allergic rhinitis includes administration of corticosteroids, antihistamines, mast cell stabilizers, nasal decongestants, anticholinergics and leukotriene antagonists.
- Intranasal medications used in the study are fluticasone furoate (27.5µg/puff) and azelastine hydrochloride 0.10%.
- The baseline total nasal symptom score, lund-kennedy endoscopic staging score, sensory attributes score and quality of life (QOL) score were comparable between the groups.
- There was a significant reduction in the total nasal symptom, endoscopic, sensory attributes and QOL scores by the day 7 when compared to baseline with both the drugs.
- The absolute eosinophil count in blood and nasal smears reduced significantly by day 15 compared to baseline in both the groups.
- Between the group analysis showed that fluticasone furoate reduced all the above scores and eosinophil count significantly compared to azelastine hydrochloride.
- Adverse effects reported were similar in both the drugs.
- Only one metered dose nasal spray of fluticasone furoate or azelastine hydrochloride was used by the patients.
- The cost of the fluticasone furoate was 235.75 rupees per patient and for azelastine hydrochloride it was 187.25 rupees per patient.

- Patients receiving fluticasone furoate had greater and sustained relief of symptoms and signs of allergic rhinitis.

Summary

Allergic Rhinitis is an IgE mediated hypersensitivity disease of the mucous membrane of nasal airway characterized by sneezing, itching, watery nasal discharge and sensation of nasal obstruction. In this study 150 patients with allergic rhinitis were randomized to receive either fluticasone furoate (27.5µg/puff) or azelastine hydrochloride (0.10%) two puffs per nostril twice daily. They were assessed for improvement in their total nasal symptom score, lund kennedy endoscopic staging score, sensory attributes score, quality of life (QOL) score and absolute eosinophil count both in blood and nasal smears at baseline and on 7^{th} and 15^{th} day. Adverse effects were also noted and cost of the treatment was analyzed.

There were 76 males and 74 females, with mean age of 26.23 ± 5.21 and 26.96 ± 4.82 years in fluticasone furoate and azelastine hydrochloride group respectively. Around 50% patients had pervious history of allergic rhinitis and symptoms aggravated with seasonal variation or in the presence of dust and smoke. The baseline total nasal symptom, endoscopic, sensory attributes and QOL scores were comparable between groups.

Patients receiving either fluticasone furoate or azelastine hydrochloride have shown significant reduction (p=0.001) in the total nasal symptom, endoscopic, sensory attributes and quality of life scores by 7^{th} day compared to baseline. Significant reduction in absolute eosinophil count both in blood and nasal smears was seen by day 15 (p=0.001). Fluticasone furoate reduced all the scores and eosinophil counts significantly compared to azelastine hydrochloride (p=0.001), a total of 33.33% and 28% reported of nasal stuffiness respectively. The cost incurred with fluticasone furoate was 235.75 rupees per patient whereas for azelastine hydrochloride it was 187.25 rupees.

Thus in our study we observed that fluticasone furoate produced sustained relief of symptoms and signs. It also reduced the absolute eosinophil count, sensory attributes and QOL scores compared to azelastine hydrochloride.

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MATERIALS AND METHODS:

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Source of data:

Study was conducted on the out-patients presenting to the Department of Otorhinolaryngology in R.L. Jalappa Hospital and Research Centre, attached to Sri Devaraj Urs Medical College, Tamaka, Kolar, from January 2012 to June 2013.

Inclusion Criteria:

1. Patients with allergic rhinitis without any complications
2. Patients of either gender aged above 12yrs
3. History of allergic rhinitis of 4 weeks or longer

Exclusion Criteria:

1. Patients with grossly deviated nasal septum or septal spur
2. Those who have undergone any recent nasal biopsy (within 2 months), nasal trauma, nasal surgery
3. Patients who have been diagnosed with atrophic rhinitis or rhinitis medicamentosa (within 2 months)
4. Those who have been treated with systemic steroids in the preceding 30 days
5. Patients who had received immunotherapy in the preceding two years
6. History of hypersensitivity to antihistaminics and corticosteroids
7. Patients with hepatic impairment
8. Pregnant and lactating women

Method of collection of data:

After the protocol was approved by institutional ethics committee, patients clinically diagnosed with allergic rhinitis by Otorhinolaryngologist were included in the study. Those patients who gave written informed consent were recruited. One hundred and fifty patients were recruited for the study and randomly divided into two groups of seventy five patients each by lottery method. Patients in group 1 received Azelastine hydrochloride (0.10%) intranasal spray (2 sprays/ nostril/ twice daily) and group 2 received Fluticasone furoate (27.5µg/spray) intranasal spray (2 sprays/ nostril/ twice daily).

Assessment was carried out on the 1st visit (baseline-Day0), first follow up (7th day) and second follow up (15th day). The patient's symptoms score was assessed using the scoring scale as mentioned below.

Total Nasal Symptom Score (subjective)[59] – Table 1

Note: Scoring (Severity scale)

0- None
1- Mild – steady symptoms but easily tolerable
2- Moderate – symptom are hard to tolerate and may interfere with activities of sleep/ daily living
3- Severe – symptoms are so bad that the person can't function all the time (day to day activities).

	Baseline (Day 0)				First Follow up (Day 7)				Day 15)			
Date												
Score / Parameter	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
1.Runny Nose												
2.Post nasal drip												
3.Nasal congestion												
4.Cough/ sore throat												
5.Sneezing												
6.Headache												
7.Nasal itching												
8.Poor smell												

Absolute eosinophil count of the nasal secretions and in blood (AEC) was done at the first visit (Baseline) at second follow up (15th day).

Absolute eosinophil count in nasal smears:[60]

SPECIMEN:

- Nasal secretions were taken from both nostrils. Mucoid gross masses were preferred over thin-watery material.
- Specimen wasobtained by swabbing the area with a thin wire swab, or by having patient blow nose on wax paper. Gross masses were used for staining.

Requirements:

- Collection device—thin wire swab, or wax paper
- Gloves, glass slide, wax pencil
- Nasal Eosinophil Stain – Hansel Stain , 95% methanol and 95% alcohol

Specimen Preparation was done as per the standard operating procedure explained below

1. Label a slide with patient information.
2. Apply specimen onto glass slide spreading it evenly. Allow smear to dry.
3. Fix sample by dipping slide in methanol for a few seconds. This step prevents specimen from coming off the slide during the staining process.
4. Using a wax pencil, draw a circle around the sample.

Staining Procedure

1. While holding slide over sink, flood slide with stain. Wait 30 seconds. Allow more time for thicker smears.
2. Add an equal volume of water to stain and wait an additional 30 seconds. For thicker smears, allow same length of time as in previous step.
3. Pour-off stain and rinse slide with distilled water. Caution: Do not squeeze water directly onto specimen area.
4. Flood slide with methanol, drain and air dry. Do not leave methanol on longer than 5 seconds. This may cause the blue stain to come off the neutrophils making them appear pink also.
5. Examine smear under microscope at a magnification of 100. Eosinophils will stain a bright red making them stand out in the field while the background will stain blue.

Interpretation:

Normally no eosinophils are present in the nasal smears. It is usually seen only in case of allergic diseases and infections.

The quality of life questionnaire was given to the patients on the first visit (Day 0), on the first follow up (Day 7) and second follow up (Day 15). The questionnaire contained the following sets of questions.

QUALITY OF LIFE QUESTIONNAIRE[59] – Table 2

1. **Activities**:

Activities	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
1.																					
2.																					

2. **Sleep**:

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubleed		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
3.Difficulty getting sleep																					
4.Lack of good night's Sleep																					

3. **Non nose/ eye symptoms**:

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
3.Headache																					
4.Thirst/ Fatigue																					

4. **Practical problems**:

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
3.Need to rub nose/ eyes																					
4.Need to blow nose repeatedly																					

5. **Nasal Symptoms**

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
9.Stuffy/Blocked																					
10.Runny Nose																					
11. Sneezing																					
12. Post nasal drip																					

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6. Eye Symptoms

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
13.Itchy eyes																					
14.Watery eyes																					

During each visit they were examined for clinical response and improvement in their symptoms based on total nasal symptom score (TNSS) and Lund and Kennedy staging system. Lund and Kennedy staging system is an objective assessment of allergic rhinitis where endoscopic examination of the nasal cavity is done and the following parameters are assesse~~d.~~

Lund and Kennedy staging system: Endoscopic appearance (objective)[61] – Table 3

	Baseline (Day 0)			First Follow up (Day 7)			End of Study (Day 15)		
Date									
Score / Parameter	**0**	**1**	**2**	**0**	**1**	**2**	**0**	**1**	**2**
1.Oedema									
2.Nasal discharge									
3.Nasal congestion									

Note: Oedema: 0- Absent, 1- Mild, 2- Severe
Discharge: 0- No discharge, 1- Clear thin discharge, 2- Thick purulent discharge
Congestion: 0- No congestion, 1- Pinkish coloured mucous membrane, 2- Purple/ Bluish coloured mucous membrane

Side effects were recorded at each visit. Cost incurred was also be analyzed by calculating the amount spent by the patient for recovery from symptoms of allergic rhinitis.

Sensory attributes[62]: Immediately following drug administration patient rated seven sensory attributes - scent, immediate taste, run down into throat, aftertaste, run off from nose, soothing feel, sneezing urge and nasal irritation within two minutes of drug administration. These were recorded through thirteen questions, response to each was noted on a seven point Likert scale. This questionnaire was adapted from previous studies comparing sensory attributes of intranasal corticosteroids.

Table 4

	Score 0	**Score 1**	**Score 2**	**Score 3**	**Score 4**	**Score 5**	**Score 6**
Did this product	None	Minimal	Mild	Moderate	Somewhat	Quite	Very

have scent?					strong	strong	strong
Are you satisfied with the scent?	Very satisfied	Quite satisfied	Somewhat satisfied	Neither	Somewhat dissatisfied	Quite dissatisfied	Very dissatisfied
Did this product have an immediate taste	None	Minimal	Mild	Moderate	Somewhat strong	Quite strong	Very strong
Are you satisfied with the taste?	Very satisfied	Quite satisfied	Somewhat satisfied	Neither	Somewhat dissatisfied	Quite dissatisfied	Very dissatisfied
Did this product have an aftertaste?	None	Minimal	Mild	Moderate	Somewhat strong	Quite strong	Very strong
Are you satisfied with the aftertaste?	Very satisfied	Quite satisfied	Somewhat satisfied	Neither	Somewhat dissatisfied	Quite dissatisfied	Very dissatisfied
Did this product run down your throat?	Not at all	Minimally	Mildly	Moderately	Somewhat markedly	Quite markedly	Very markedly
Did this product run off your nose?	Not at all	Minimally	Mildly	Moderately	Somewhat markedly	Quite markedly	Very markedly
Did the product fee soothing?	Very markedly	Quite markedly	Somewhat markedly	Moderately	Mildly	Minimally	None
Did the product make you want to sneeze?	Not at all	Minimally	Mildly	Moderately	Somewhat markedly	Quite markedly	Very markedly
Did this product cause irritation of the nose?	Not at all	Minimally	Mildly	Moderately	Somewhat markedly	Quite markedly	Very markedly
How satisfied are you with this product?	Very satisfied	Quite satisfied	Somewhat satisfied	Neither	Somewhat dissatisfied	Quite dissatisfied	Very dissatisfied

How likely are you to comply with the product if prescribed?	Very likely	Quite likely	Somewhat likely	Neither	Somewhat unlikely	Quite unlikely	Very unlikely

STATISTICAL METHODS:

Sample size calculation:

To detect a mean difference of 1.05 in the total nasal symptom score on day 15 with the effect size of 0.8, α error of 5%, with 80% power and 10% drop out rate the sample size required in each group was 65.

The demographic details were analyzed using descriptive statistics. Absolute eosinophil count was assessed using paired and unpaired student‘t’ test for within and between the groups respectively. The symptom scores (TNSS) and quality of life questionnaire scores (RQLQ) were analyzed using paired and unpaired student t test for within and between the groups respectively. Side effects were assessed using Chi Square test. Cost incurred was analyzed using unpaired student‘t’ test. ‘p’ value of <0.05 was considered significant

Key to mater chart

Sl no	-	Serial number
M	-	Male
F	-	Female
AEC1	-	Absolute eosinophil count in blood at baseline
AEC2	-	Absolute eosinophil count in blood on day 15
AEC3	-	Absolute eosinophil count in nasal smears at baseline
AEC4	-	Absolute eosinophil count in nasal smears on day 15
TNSS0	-	Total nasal symptom score at baseline
TNSS1	-	Total nasal symptom score on day 7
TNSS2	-	Total nasal symptom score on day 15
LKSS0	-	Lund kennedy endoscopic staging score at baseline
LKSS1	-	Lund kennedy endoscopic staging score on day 7
LKSS2	-	Lund kennedy endoscopic staging score on day 15
QOL0	-	Quality of life score at baseline
QOL1	-	Quality of life score on day 7
QOL2	-	Quality of life score on day 15
SA0	-	Sensory attributes score at baseline
SA1	-	Sensory attributes score on day 7
SA2	-	Sensory attributes score on day 15
HPF	-	High power field

PROFORMA

OP No.: Date:

Serial No.:

1. Name: 2. Age: 3. Sex:
4. Occupation: 5. Educational Status:
6. Address:

Phone No: Residence: Mobile:

7. Complaints:

   Symptoms: Rhinorrhea/ nasal obstruction/ sneezing
   Duration
   Aggravating Factors
   Seasonal Variation

8. Family History of Asthma:
   Personal History: smoking/alcohol/drug intake/DM/HTN/Bronchial Asthma.

9. General Physical Examination:
   CVS
   RS
   CNS

10. Examination of the Nose/Upper respiratory tract

Sl. No	Examination	Right side	Left side
1	External nose and vestibule		
2	Nasal passage		
3	Septum		
4	Lateral wall		
	a. Turbinates		
	b. Mucosa		

11. Diagnosis

12. Treatment with dosage:

13. Informed consent taken or not

FOLLOW UP VISITS:

1. **Absolute eosinophil count**

	Baseline (Day 0)	Day 15)
Parameter Absolute eosinophil count: **a)** Nasal Smears		
b) Blood		

2. <u>Total Nasal Symptom Score (subjective)</u>

<u>Note:</u> Scoring (Severity scale)

0- None
1- Mild – steady symptoms but easily tolerable
2- Moderate – symptom are hard to tolerate and may interfere with activities of sleep/ daily living
3- Severe – symptoms are so bad that the person can't function all the time.

	Baseline (Day 0)				First Follow up (Day 7)				Day 15)			
Date												
Score / Parameter	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**	**0**	**1**	**2**	**3**
1.Runny Nose												
2.Post nasal drip												
3.Nasal congestion												
4.Cough/ sore throat												
5.Sneezing												
6.Headache												
7.Nasal itching												
8.Poor smell												

3. <u>Lund and Kennedy staging system: Endoscopic appearance (objective)</u>

	Baseline (Day 0)			First Follow up (Day 7)			End of Study (Day 15)		
Date									
Score / Parameter	**0**	**1**	**2**	**0**	**1**	**2**	**0**	**1**	**2**
1.Oedema									
2.Nasal discharge									
3.Nasal congestion									

Oedema: 0- Absent, 1- Mild, 2- Severe
Discharge: 0- No discharge, 1- Clear thin discharge, 2- Thick purulent discharge
Congestion: 0- No congestion, 1- Pinkish coloured mucous membrane, 2- Purple/ Bluish coloured mucous membrane

4. **QUALITY OF LIFE QUESTIONNAIRE**

1. **Activities**:

Activities	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
1.																					
2.																					

2. **Sleep**:

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
3.Difficulty getting sleep																					
4.Lack of good night's Sleep																					

3. **Non nose/ eye symptoms**:

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
3.Headache																					
4.Thirst/ Fatigue																					

4. **Practical problems**:

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
3.Need to rub nose/ eyes																					
4.Need to blow nose repeatedly																					

5. Nasal Symptoms

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
9.Stuffy/Blocked																					
10.Runny Nose																					
11. Sneezing																					
12. Post nasal drip																					

6. Eye Symptoms

	Not troubled			Hardly Troubled			Somewhat troubled			Moderately troubled			Quite a bit troubled			Very troubled			Extremely Troubled		
	0			1			2			3			4			5			6		
Day / Act.	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**	**0**	**7**	**15**
13.Itchy eyes																					
14.Watery eyes																					

INFORMED CONSENT FORM

COMPARATIVE STUDY OF EFFICACY AND SAFETY OF INTRANASAL AZELASTINE HYDROCHLORIDE AND FLUTICASONE FUROATE IN TREATMENT OF ALLERGIC RHINITIS

Allergic rhinitis is a chronic disease that affects productivity and quality of life characterized by sneezing, nasal itch, rhinorrhea and congestion. Use of intranasal Azelastine hydrochloride and Fluticasone furoate helps to control the further progress of the disease and provides symptomatic relief.

If you agree to participate in the study we will collect information (as per proforma) from you or a person responsible for you or both. We will collect the treatment and relevant details from your hospital record. Following treatment follow up will be done on day 7 and 15. This information collected will be used for only dissertation and publication. This study has been reviewed by the institutional ethical committee. There is no compulsion to agree to this study. The care you will get will not change if you don't wish to participate. You are required to sign/ provide thumb impression only if you voluntarily agree to participate in this study.

I understand that I remain free to withdraw from the study at any time and this will not change my future care. I have read or have been read to me and understand the purpose of the study, the procedure that will be used, the risk and benefits associated with my involvement in the study and the nature of information that will be collected and disclosed during the study. I have had the opportunity to ask my questions regarding various aspects of the study and my questions are answered to my satisfaction. I the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information for dissertation.

Subject name and signature/ Thumb impression DATE:

Parents / Guardians name / Thumb impression DATE:

Signature of the person taking consent DATE:

RESULTS

A total of 150 patients who satisfied the inclusion criteria and clinically diagnosed to be suffering from allergic rhinitis by an Otorhinolaryngologist were recruited for this study after obtaining their written informed consent. The commonest symptoms which the patient presented to the outpatient department were sneezing, rhinorrhea and nasal obstruction. Patients were randomized into two groups Group A (n=75) which received intranasal Fluticasone furoate spray (27.5 µg/spray, two sprays per nostril twice daily) and Group B (n=75) which received intranasal Azelastine hydrochloride spray (0.10%, two sprays per nostril twice daily). All 150 patients completed the study.

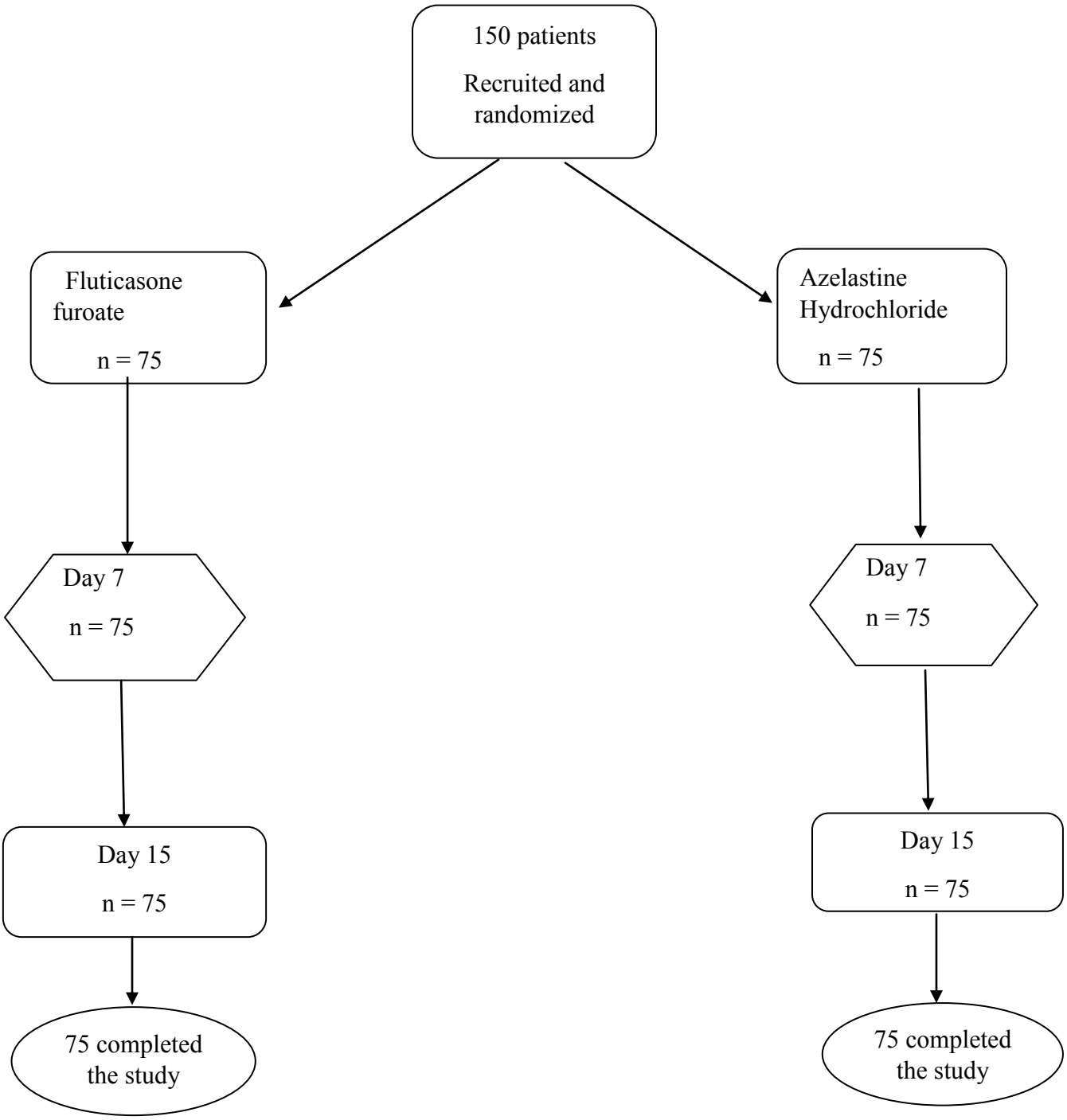

Fig 12. Consort chart showing patient's recruitment and follow up

Table 5 – Gender wise distribution of subjects

Characteristics	Male	Female	Total no. of patients
Fluticasone furoate	39	36	75
Azelastine hydrochloride	37	38	75
Total	76	74	150

52% and 48% males and females received fluticasone furoate whereas Azelastine hydrochloride was received by 49.3% and 50.7% respectively.

Table 6: Demographic data

Characteristics	Age in years Mean ± SD	Similar complaints in the past	Aggravating factors (No. of patients)
Fluticasone furoate	26.23 ± 5.21	42/75	Dust, smoke – 34 Cold, winter – 23
Azelastine hydrochloride	26.96 ± 4.82	34/75	Dust, smoke – 30 Cold, winter – 21

The mean age of the patients in both the groups was comparable. (p value – 0.89). The patients who had previous history of allergic rhinitis was 56% and 45% in fluticasone furoate and azelastine hydrochloride group.

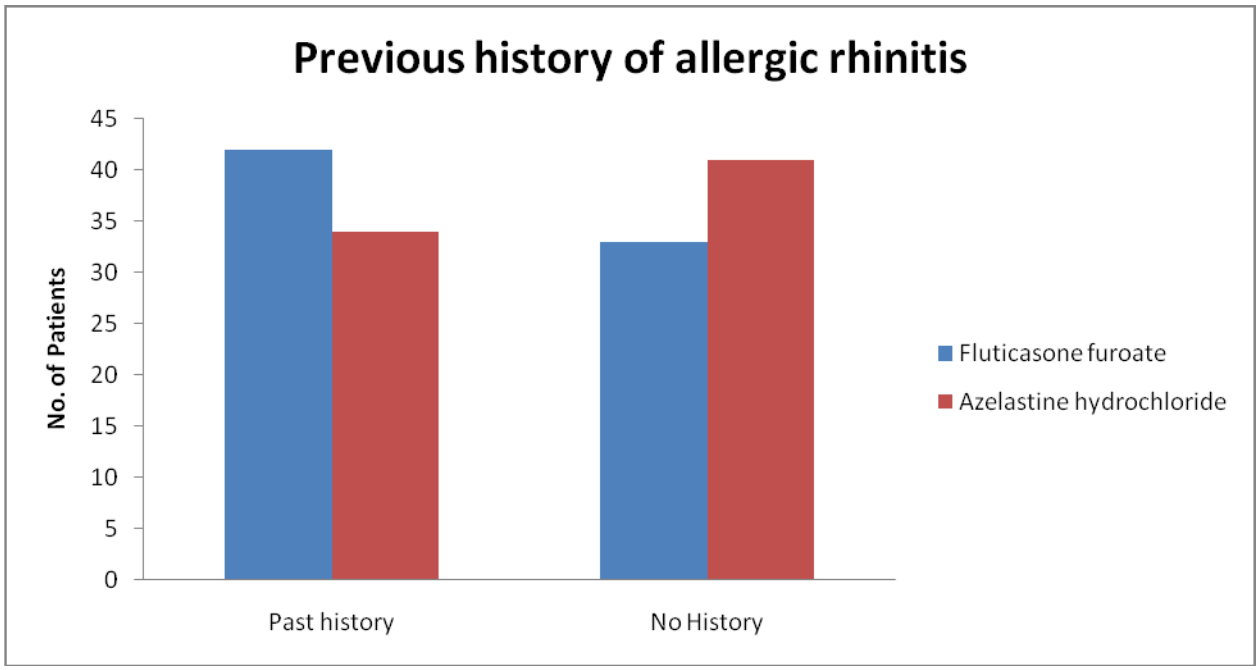

Figure 13: Past history of allergic rhinitis

Table 7: Baseline characteristics

Baseline characteristics	**Fluticasone furoate**		**Azelastine hydrochloride**		**p value**
	Mean ± SD	**Median (Range)**	**Mean ± SD**	**Median (Range)**	
Total nasal symptom score	10.13 ± 0.79	10 (8-11)	10.07 ± 0.70	10 (9-11)	0.58
Lund Kennedy endoscopic staging score	5.13 ± 0.68	5 (4-6)	4.92 ± 0.69	5 (4-6)	0.60
Absolute eosinophil count in blood (cells/cumm)	421.67 ± 32.66	-	433.27 ± 32.79	-	0.03
Absolute eosinophil count in nasal smears (cells/100HPF)	5.17 ± 0.92	5 (2-6)	4.65 ± 1.35	5 (2-6)	0.007
Quality of life questionnaire	36.63 ± 3.07	36 (30-43)	36.80 ± 2.47	37 (32-42)	0.70
Sensory attributes	34.12 ± 4.23	33 (27-45)	34.71 ± 3.55	35.5 (27-41)	0.42

Baseline characteristics were comparable between the groups except absolute eosinophil count.

Table 8: Individual scores of each parameter of total nasal symptom score

Characteristics	Fluticasone furoate Mean ± SD {Median}			Azelastine Hydrochloride Mean ± SD {Median}		
	Day 0	Day 7	p value	Day 0	Day 7	p value
Runny Nose	2 ± 0 {2}	0 {0(0)}	0.001*	2±0 {2}	0.73±0.46 {1}	0.001*
Post Nasal drip	1.11±0.33 {1}	0.22±0.44 {0}	0.001*	1.09±0.30 {1}	0.82±0.40 {1}	0.001*
Nasal congestion	2.11±0.33 {2}	0.89±0.33 {1}	0.001*	2±0 {2}	0.82±0.40 {1}	0.001*
Sore throat/Cough	0.78±0.44 {1}	0.11±0.33 {1}	0.001*	0.91±0.30 {1}	0 {0}	0.001*
Sneezing	2±0 {2}	0.78±0.44 {1}	0.001*	1.91±0.30 {2}	0.82±0.40 {1}	0.001*
Headache	1±0 {1}	0.44±0.52 {0}	0.001*	0.91±0.30 {1}	0.36±0.50 {0}	0.001*
Nasal irritation	0.56±0.52 {1}	0.11±0.33 {0}	0.001*	0.82±0.40 {1}	0.36±0.50 {0}	0.001*
Poor smell	0.11±0.33 {0}	0 {0}	0.001*	0.09±0.30 {1}	0 {0}	0.001*
Total nasal symptom score	10.13 ± 0.79 {10}	2.89 ± 0.70 {3}	0.001*	10.07 ± 0.70 {10}	3.84 ± 0.78 {4}	0.001*

When compared to baseline there was significant decrease (p=0.001) in the scores of all the individual parameters of the total nasal symptom score by day 7 in both the groups and by day 15 the scores of the various parameters reduced to zero with both the drugs. Between the group analysis showed reduction was greater in patients receiving fluticasone furoate (p =0.001) by day 7.

Table 9: Lund Kennedy endoscopic staging

Characteristics	**Endoscopic staging Mean ± SD {Median (Range)}**			**p value**
	Day 0	**Day 7**	**Day 15**	
Fluticasone furoate	5.13 ± 0.68 {5 (4-6)}	1.35 ± 0.55 {1 (0-2)}	0	0.001*
Azelastine hydrochloride	4.92 ± 0.69 {5 (4-6)}	2.24 ± 0.75 {2 (1-3)}	0	0.001*
p value	0.60	0.001*	1.000	

Reduction in Lund Kennedy endoscopic staging score was seen in both the groups, but fluticasone furoate significantly reduced the scoring when compared to Azelastine hydrochloride by day 7 (p=0.001).

Table 10: Absolute eosinophil count in blood and nasal smears

Characteristics	AEC – Blood Cells/cumm Mean ± SD		p value	AEC - Nasal Smears Cells/HPF Mean ± SD		p value
	Day 0	Day 15		Day 0	Day 15	
Fluticasone furoate	421.67 ± 32.66	199.60 ± 20.75	0.001*	5.17 ± 0.92	0.25 ± 0.43	0.001*
Azelastine hydrochloride	433.27 ± 32.79	220.33 ± 23.26	0.001*	4.65 ± 1.35	0.60 ± 0.49	0.001*
p value	0.03	0.001*		0.007	0.001*	

Within the group there was reduction in the eosinophil count by day 15 when compared to baseline. Fluticasone furoate significantly reduced the absolute eosinophil count both in blood and nasal smears when compared to azelastine hydrochloride by day 15 (p =0.001). Absolute eosinophil count in the nasal smears ranged between zero to one in both the groups by day 15, but the number of patients who had a count of zero was more with fluticasone furoate (56) than azelastine hydrochloride (30).

Table 11: Quality of Life questionnaire

Characteristics	**Quality of life questionnaire Mean ± SD {Median (range)}**			**p value**
	Day 0	**Day 7**	**Day 15**	
Fluticasone furoate	36.63 ± 3.07 {36 (30-43)}	11.75 ± 2.32 {12 (7-17)}	0	0.001*
Azelastine hydrochloride	36.80 ± 2.47 {37 (32-42)}	17.32 ± 2.95 {17 (11-23)}	0	0.001*
p value	0.70	0.001*	1.000	

There was a significant reduction in the patient satisfaction score in both the groups. Fluticasone furoate significantly decreased the score when compared to Azelastine hydrochloride at the end of day 7 (p=0.001) which denotes significant improvement in quality of life.

Table 12: Sensory attributes

Characteristics (116 patients)	**Sensory attributes Mean ± SD {Median (range)} Immediately following drug administration**			**p value**
	Day 0	**Day 7**	**Day 15**	
Fluticasone furoate (n = 58)	34.12 ± 4.23 {33 (27-45)}	9.74 ± 2.37 {9 (6-16)}	0	0.001*
Azelastine hydrochloride (n = 58)	34.71 ± 3.55 {35.5 (27-41)}	11.71 ± 2.69 {11.5 (6-19)}	0	0.001*
p value	0.42	0.001*	1.000	

Sensory attributes (Table 4) were assessed in 116 patients i.e. 58 patients in each group within two minutes of drug administration on follow up visits. The above table shows intragroup reduction which was significant. Fluticasone furoate had higher reduction in the scores when compared to Azelastine hydrochloride at the end of day 7 which was statistically significant (p=0.001).

Adverse effects:

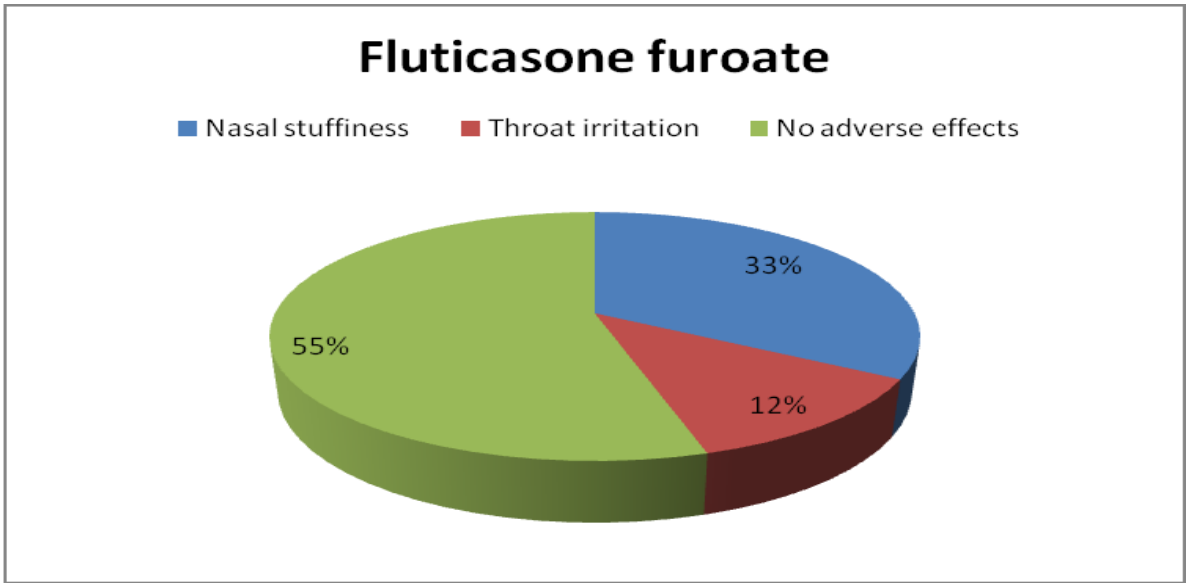

Figure 14: Adverse effects of fluticasone furoate

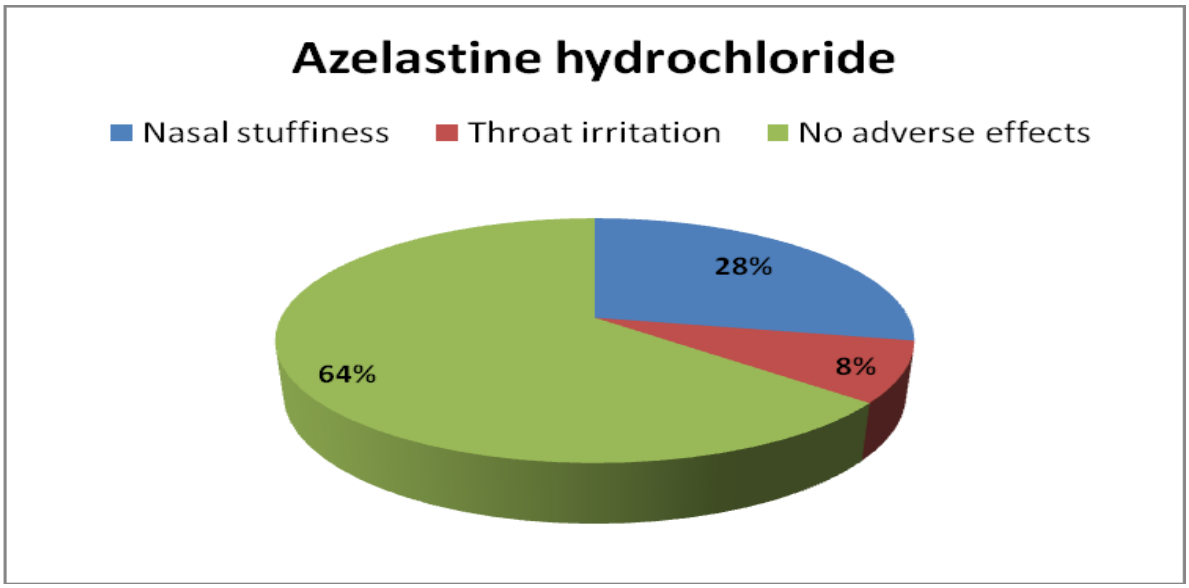

Figure 15: Adverse effects of azelastine hydrochloride

Nasal stuffiness was one of the commonest adverse effect encountered during the study period. 33.33% of patients presented with nasal stuffiness with Fluticasone furoate whereas it was 28% with Azelastine hydrochloride. 12% and 8% patients receiving Fluticasone furoate and Azelastine hydrochloride respectively reported of minimal throat irritation till day 7.

COST OF THE TREATMENT:

One intranasal spray of Fluticasone furoate was 235.75 rupees. Each patient required only metered spray in this study,so the cost per patient was Rs. 235.75. Whereas one intranasal Azelastine hydrochloride spray was 187.25 rupees. All patients in this group also required only one metered spray, so the cost per patient was Rs. 187.25.

Sl. No.	Name	Age	Gender	Complaints	AEC 1	AEC 2	AEC 3	AEC Nasal Smear (Day 0)	AEC 4	AEC Nasal Smear (Day 15)	TNSS 0	TNSS 1	TNSS 2	LKSS 0	LKSS 1	LKSS 2	QOL 0	QOL 1	QOL 2	SA 0	SA 1	SA 2
1	Champa devi	28	F	Rhinorrhea,Nasal obstruction,Sneezing	385	170	6	4-6/100HPF	1	0-1/100HPF	8	3	0	5	1	0	36	11	0			
2	Shilpa	20	F	Sneezing	410	180	6	4-6/100HPF	0	0/100HPF	8	2	0	5	1	0	37	11	0			
3	Yallappa	44	M	Sneezing	375	195	4	3-4/100HPF	0	0/100HPF	11	3	0	5	1	0	43	10	0			
4	Prema	24	F	Sneezing,nasal obstruction	415	190	5	4-5/100HPF	0	0/100HPF	10	2	0	5	0	0	34	15	0			
5	Radhakrishna	30	M	Rhinorrhea,Nasal obstruction	405	190	6	5-6/100HPF	0	0/100HPF	11	3	0	6	1	0	36	17	0			
6	Somashekar	36	M	Nasal obstruction,sneezing	380	210	6	4-6/100HPF	0	0/100HPF	10	3	0	5	1	0	36	11	0			
7	Aravind kumar	37	M	Nasal obstruction,sneezing	390	185	5	3-5/100HPF	0	0/100HPF	10	4	0	5	1	0	35	10	0			
8	Venkatesh	40	M	Rhinorrhea,Nasal obstruction,Sneezing	390	200	5	3-5/100HPF	0	0/100HPF	10	2	0	5	1	0	33	9	0			
9	Afra Farheen	21	F	Nasal obstruction,sneezing	425	180	6	4-6/100HPF	0	0/100HPF	9	2	0	5	1	0	32	7	0			
10	Nandini	24	F	Rhinorrhea,sneezing	430	180	5	3-5/100HPF	0	0/100HPF	11	3	0	6	2	0	39	14	0			
11	Samyutka	28	F	Nasal obstruction,sneezing	440	210	6	4-6/100HPF	1	0-1/100HPF	10	4	0	5	2	0	37	13	0			
12	Vijay	29	M	Sneezing	410	170	5	2-5/100HPF	0	0/100HPF	10	3	0	5	1	0	38	10	0			
13	Jayachandra	37	M	Nasal obstruction	390	180	4	3-4/100HPF	1	0-1/100HPF	10	4	0	6	2	0	40	15	0			
14	Manjunath	30	M	Rhinorrhea	400	190	6	3-6/100HPF	0	0/100HPF	11	4	0	5	2	0	39	12	0			
15	Waheeda Begum	28	F	nasal obstruction	415	180	6	4-6/100HPF	0	0/100HPF	10	2	0	5	1	0	38	11	0			
16	Pavithra	30	F	Sneezing	370	190	4	2-4/100HPF	1	0-1/100HPF	10	4	0	6	2	0	33	10	0			
17	Gautham	24	M	Rhinorrhea,Nasal obstruction,Sneezing	425	205	6	3-6/100HPF	1	0-1/100Hpf	11	3	0	5	2	0	35	15	0			
18	Shankar	24	M	Rhinorrhea, sneezing, nasal obstruction	440	210	6	4-6/100HPF	1	0-1/100HPF	11	3	0	6	1	0	36	12	0	38	12	0
19	Naveen	24	M	Nasal obstruction	475	225	4	3-4/100HPF	0	0/100HPF	10	2	0	6	1	0	39	14	0	29	7	0
20	Rajgopal	27	M	Sneezing	425	200	5	2-5/100HPF	0	0/100HPF	11	4	0	5	2	0	37	11	0	27	9	0
21	Sushmitha	21	F	Rhinorrhea	415	175	6	3-6/100HPF	0	0/100HPF	10	3	0	4	2	0	35	14	0	33	8	0
22	Simon	30	M	Sneezing, Rhinorrhea	395	185	6	2-6/100HPF	0	0/100HPF	10	3	0	4	1	0	42	15	0	35	9	0
23	Pradeep	23	M	Sneezing	370	200	6	4-6/100HPF	0	0/100HPF	10	4	0	6	1	0	32	11	0	39	7	0
24	Chandrakala	21	F	Nasal obstruction	490	230	4	3-4/100HPF	0	0/100HPF	9	2	0	6	2	0	43	14	0	41	12	0
25	Shankari	34	F	Nasal obstruction, Rhinorrhea, Sneezing	470	210	6	5-6/100HPF	0	0/100HPF	10	2	0	4	1	0	38	13	0	43	15	0
26	Bhavin kumar	24	M	Sneezing	460	245	4	2-4/100HPF	0	0/100HPF	11	4	0	5	2	0	39	12	0	45	13	0
27	Vijay Kumar	27	M	Nasal obstruction	475	235	6	3-6/100HPF	0	0/100HPF	11	3	0	6	1	0	40	14	0	42	14	0
28	Muniyappa	32	M	Rhinorrhea	430	240	5	2-5/100HPF	1	0-1/100HPF	10	3	0	5	1	0	35	10	0	37	10	0
29	Munirathnamma	28	F	Sneezing, Nasal obstruction	415	210	5	3-5/100HPF	0	0/100HPF	9	3	0	4	2	0	34	10	0	34	7	0
30	Ravi	22	M	Sneezing	385	195	3	2-3/100HPF	1	0-1/100HPF	9	2	0	4	1	0	35	9	0	33	8	0
31	Geetha	24	F	Nasal Obstruction	400	230	5	3-5/100HPF	0	0/100HPF	10	2	0	5	1	0	34	7	0	32	10	0
32	Narayanamma	24	F	Nasal obstruction, Rhinorrhea, Sneezing	415	220	6	4-6/100HPF	0	0/100HPF	11	4	0	5	1	0	38	11	0	36	11	0
33	Asma taj	21	F	sneezing	450	175	6	4-6/100HPF	1	0-1/100HPF	11	3	0	5	2	0	32	7	0	35	12	0
34	Ramesh	24	M	Rhinorrhea	370	230	6	3-6/100HPF	1	0-1/100Hpf	10	2	0	6	1	0	36	10	0	31	10	0
35	Savitha	27	F	Sneezing, Rhinorrhea	465	240	4	2-4/100HPF	0	0/100HPF	9	2	0	6	2	0	39	12	0	30	9	0
36	Anand	28	M	Nasal obstruction, Rhinorrhea, Sneezing	435	190	4	3-4/100HPF	0	0/100HPF	11	3	0	5	1	0	37	11	0	29	8	0
37	Kalavathi	23	F	Rhinorrhea, Nasal obstruction	445	185	3	2-3/100HPF	0	0/100HPF	10	2	0	4	0	0	40	12	0	28	8	0
38	Manjunath	24	M	Sneezing	480	210	5	3-5/100HPF	0	0/100HPF	9	3	0	6	2	0	32	7	0	35	10	0
39	Ambika	24	F	Sneezing, Rhinorrhea	380	195	6	4-6/100HPF	1	0-1/100HPF	11	2	0	4	0	0	30	7	0	37	11	0
40	Pramila	21	F	Nasal obstruction	425	230	4	3-4/100HPF	0	0/100HPF	11	3	0	5	1	0	39	10	0	38	12	0
41	Kunal	24	M	Sneezing	390	180	4	3-4/100HPF	1	0-1/100HPF	10	4	0	6	1	0	38	7	0	32	8	0
42	Sameer	26	M	Rhinorrhea	425	180	5	4-5/100HPF	0	0/100HPF	11	3	0	6	2	0	33	14	0	36	10	0
43	Saraswathi	30	F	Sneezing, Rhinorrhea	430	210	6	5-6/100HPF	0	0/100HPF	10	3	0	5	2	0	35	13	0	34	7	0
44	Zuhaib	29	M	Sneezing	440	170	6	4-6/100HPF	0	0/100HPF	10	4	0	4	1	0	36	10	0	31	9	0
45	Anamika	21	F	Nasal obstruction	410	180	5	3-5/100HPF	0	0/100HPF	11	2	0	4	1	0	39	15	0	37	8	0
46	Ankita	24	F	Nasal obstruction, Rhinorrhea, Sneezing	390	190	5	3-5/100HPF	0	0/100HPF	11	2	0	6	2	0	37	12	0	32	8	0
47	Sinchana	27	F	Sneezing	400	180	6	4-6/100HPF	0	0/100HPF	10	4	0	6	2	0	35	11	0	31	9	0
48	Rakshita	28	F	Nasal obstruction	415	190	5	3-5/100HPF	0	0/100HPF	11	3	0	4	1	0	42	10	0	30	10	0
49	Ramu	32	M	Rhinorrhea	370	185	6	4-6/100HPF	0	0/100HPF	10	3	0	5	1	0	32	15	0	28	8	0

50	Ashish	21	M	Sneezing, Nasal obstruction	425	200	5	2-5/100HPF	0	0/100HPF	10	3	0	6	2	0	43	12	0	28	6	0
51	Abhimanyu	24	M	Sneezing	440	180	4	3-4/100HPF	1	0-1/100HPF	10	2	0	5	1	0	38	14	0	31	6	0
52	Abhinav	20	M	Nasal Obstruction	475	180	6	3-6/100HPF	0	0/100HPF	9	2	0	4	2	0	39	11	0	30	7	0
53	Muniyappa	35	M	Nasal obstruction, Rhinorrhea, Sneezing	425	210	6	4-6/100HPF	0	0/100HPF	10	4	0	4	1	0	40	14	0	33	7	0
54	Gowramma	36	F	sneezing	415	170	4	2-4/100HPF	0	0/100HPF	11	3	0	5	1	0	35	15	0	37	8	0
55	Leelamma	32	F	Rhinorrhea	395	180	6	3-6/100HPF	0	0/100HPF	11	2	0	5	2	0	34	11	0	32	8	0
56	Priya	26	F	Sneezing, Rhinorrhea	370	190	6	4-6/100HPF	0	0/100HPF	10	2	0	5	1	0	35	14	0	33	9	0
57	Arpana	25	F	Rhinorrhea,Nasal obstruction,Sneezing	425	180	6	4-6/100HPF	0	0/100HPF	9	3	0	6	1	0	34	13	0	36	11	0
58	Archana	23	F	Sneezing	440	190	4	3-4/100HPF	0	0/100HPF	9	2	0	6	1	0	38	12	0	34	10	0
59	Swetha	26	F	Sneezing	475	205	5	2-5/100HPF	0	0/100HPF	10	3	0	5	2	0	32	14	0	33	9	0
60	Ayush	20	M	Sneezing,nasal obstruction	425	210	6	3-6/100HPF	0	0/100HPF	11	2	0	4	1	0	36	10	0	31	9	0
61	Nagraj	30	M	Rhinorrhea,Nasal obstruction	415	225	6	2-6/100HPF	1	0-1/100HPF	11	3	0	5	2	0	39	10	0	37	12	0
62	Bharath	21	M	Nasal obstruction,sneezing	395	200	6	4-6/100HPF	0	0/100HPF	10	3	0	5	1	0	37	9	0	39	13	0
63	Bhoomika	22	F	Nasal obstruction,sneezing	370	175	4	3-4/100HPF	1	0-1/100HPF	9	4	0	6	2	0	40	12	0	40	12	0
64	Vimal	20	M	Rhinorrhea,Nasal obstruction,Sneezing	490	185	6	5-6/100HPF	0	0/100HPF	11	2	0	5	1	0	32	11	0	41	13	0
65	Narayanswamy	30	M	Nasal obstruction,sneezing	470	200	4	2-4/100HPF	0	0/100HPF	10	2	0	5	1	0	32	10	0	33	7	0
66	Harish	26	M	Rhinorrhea,sneezing	460	230	6	3-6/100HPF	1	0-1/100HPF	9	3	0	5	2	0	43	15	0	36	9	0
67	Chandrica	23	F	Nasal obstruction,sneezing	475	210	5	2-5/100HPF	1	0-1/100Hpf	9	4	0	5	2	0	38	12	0	35	12	0
68	Chandana	21	F	Sneezing	430	245	5	3-5/100HPF	0	0/100HPF	10	3	0	6	1	0	39	14	0	29	10	0
69	Chandrappa	29	M	Nasal obstruction	415	235	3	2-3/100HPF	0	0/100HPF	11	4	0	5	1	0	40	11	0	41	16	0
70	Ramya	21	F	Rhinorrhea	385	240	5	3-5/100HPF	0	0/100HPF	11	4	0	5	2	0	35	14	0	38	14	0
71	Lakshmi	20	F	nasal obstruction	400	210	6	4-6/100HPF	0	0/100HPF	10	2	0	6	1	0	34	15	0	32	11	0
72	Varun	20	M	Sneezing	415	195	6	4-6/100HPF	1	0-1/100HPF	9	4	0	5	2	0	35	11	0	33	13	0
73	Abhishek	22	M	Rhinorrhea,Nasal obstruction	450	200	6	3-6/100HPF	0	0/100HPF	11	3	0	5	1	0	34	12	0	31	10	0
74	Hari	21	M	Nasal obstruction,sneezing	460	180	4	2-4/100HPF	1	0-1/100HPF	10	3	0	6	2	0	36	11	0	30	8	0
75	Jayshree	25	F	Nasal obstruction,sneezing	450	210	4	3-4/100HPF	0	0/100HPF	11	2	0	5	1	0	39	13	0	28	6	0

LIST OF ABBREVIATIONS

AR – Allergic rhinitis

AH- Azelastine hydrochloride

FF – Fluticasone furoate

TNSS – Total nasal symptom score

RQLQ – Rhinoconjunctivitis quality of life questionnaire

QOL – Quality of life

AEC – Absolute eosinophil count

ARIA – Allergic rhinitis and its impact on asthma

LPR – Late phase reaction

AED – Aerodynamic equivalent diameter

FDA – Food and drug administration

IL – Interleukins

TGF-B – Transforming growth factor beta

Th – T lymphocyte helper cells

ICAM – Intracellular adhesion molecule

GM-CSF – Granulocyte monocyte colony stimulating factor

DNS – Deviated nasal septum

SRS-A – Slow reacting substance of anaphylaxis

WHO – World health organization

RAST – Radioallergic sorbent assay

Ig – Immunoglobulins

HPA – Hypothalamo-pituitary adrenal axis

ABSTRACT

BACKGROUND

Allergic rhinitis (AR) is a common disease characterized by nasal itch, sneezing, watery or mucous rhinorrhea and nasal obstruction. It is a chronic disease representing approximately 20% of the general population. Patients with allergic rhinitis can experience fatigue, sleep disturbances, social function impairment, depression, anxiety, learning and attention (cognitive) impairment, increased school absenteeism, and decreased work efficiency. Therefore, if untreated can substantially impair patients overall quality of life. Apart from the local disease, allergic rhinitis can cause considerable morbidity including chronic sinusitis and otitis. Treatment options of allergic rhinitis include intranasal corticosteroids, oral or intranasal antihistaminics, oral leukotriene antagonists, intranasal cromoglycate, nasal decongestants and allergen immunotherapy. Azelastine hydrochloride (antihistaminic) and Fluticasone furoate (steroid) are available as intranasal formulations and are said to be effective in controlling allergic rhinitis. There is paucity of comparative data of intranasal Azelastine hydrochloride and Fluticasone furoate in treatment of allergic rhinitis in India. Hence, this study was planned to compare the efficacy and safety of these drugs in treatment of allergic rhinitis.

OBJECTIVES OF STUDY

1. To study the efficacy of Intranasal Azelastine hydrochloride and Fluticasone furoate in allergic rhinitis
2. To study the safety profile of Azelastine hydrochloride and Fluticasone furoate in allergic rhinitis
3. To analyze the cost incurred with the use of the above drugs in allergic rhinitis

MATERIALS AND METHODS

The study was conducted on outpatients presenting to the Department of Otorhinolaryngology at R L Jalappa Hospital and Research Centre and SNR Hospital, attached to Sri Devaraj Urs Medical College, Tamaka, Kolar, Karnataka from January 2012 to June 2013. 150 patients of either gender were included for the study and divided into two groups of 75

patients each each to receive either fluticasone furoate (27.5µg/puff) or azelastine hydrochloride (0.10%) intranasally. Informed consent was taken from the patient. Detailed clinical examination and necessary investigation was done before starting the therapy. Assessment in terms of absolute eosinophil count, symptoms (total nasal symptom score), signs (diagnostic nasal endoscopic staging), quality of life (QOL) and sensory attributes were done at baseline, day 7 and 15. Adverse effects were recorded and cost incurred analyzed.

The demographic details were analyzed using descriptive statistics. Absolute eosinophil count, symptom scores (TNSS) and quality of life questionnaire scores (RQLQ) was assessed using paired and unpaired student't' test for within and between the groups respectively. Adverse effects were recorded and cost incurred was analyzed. 'p' value of <0.05 was considered significant

RESULTS:

Study involved 150 patients (76 males and 74 females) with a mean age of 26.23± 5.2 years (FF) & 26.96 ± 4.8 years (AH). Baseline parameters were comparable between groups. Reduction of all scores was seen in both the groups by day 7 but when compared between groups reduction in fluticasone furoate was significant (p=0.001). There was significant reduction (p=0.001) in absolute eosinophil count both in blood and nasal smears by day 15 in both the groups, but between the groups reduction was significant (p=0.001) with fluticasone. Adverse reactions reported were 33.33% (FF) and 28% (AH). Cost of fluticasone was Rs 235.75/patient and azelastine Rs 187.25/patient.

CONCLUSION:

Fluticasone furoate produced sustained relief of symptoms, signs, reduced QOL and sensory attributes scores with greater reduction in eosinophil count in allergic rhinitis patients compared to azelastine hydrochloride.

Key words: Allergic rhinitis, efficacy, intranasal spray, fluticasone furoate azelastine hydrochloride.

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