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Validation of guinea pig model of allergic rhinitis by oral and topical drugs

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Abstract

Ovalbumin-induced guinea pig model of rhinitis was assessed for its utility in the studies of rhinitis. Systemic sensitization and challenge with ovalbumin-induced rhinitis symptoms and an increase in anti-OVA-IgE and IgG titers, positive skin reactions and nasal lavage IL-4 concentration. Histopathology of nasal mucosa showed infiltration of eosinophils and other inflammatory cells consistent with the symptoms. Topical sensitization of ovalbumin yielded inconsistent symptoms of rhinitis. In systemic sensitization model, repeated challenge of ovalbumin caused similar response for at least 3 consecutive challenges. The symptoms were affected by relative humidity in the air and dosing volume of topical drugs. Sneezing and lacrimation were reduced by acute oral administration of the H_1 receptor antagonists and steroids or the prophylactic oral administration of cysteinyl leukotriene ($CysLT_1$) receptor antagonist montelukast or acute topical antihistamines, mast cell stabilizer sodium cromoglycate and anticholinergic agent ipratropium bromide, but not by a topical steroid. Nose rubbing was reduced significantly by some oral and topical antihistamines. Oral steroids offered excellent protection against all symptoms. Dexamethasone and montelukast also inhibited nasal lavage IL-4 concentration and inflammatory cell infiltration. Treatment with topical steroid fluticasone for 2 weeks had no effect on sneezing or rubbing. However, it caused complete inhibition of congestion. The cyclooxygenase inhibitor indomethacin had no effect on symptoms of rhinitis. The adrenergic α receptor agonist-decongestant oxymetazoline caused reduction in congestion. These results suggest that differential responsiveness to symptoms of rhinitis by a new agent can be very well profiled in the model in congruence with the mediation pathways and mechanism of action of drugs. The model provides complete symptomatic characterization of rhinitis and is a good tool for its study.

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1. Introduction

Allergic rhinitis is an IgE-mediated inflammatory disease of the nasal mucosal membrane characterized mainly by the early phase response exhibiting symptoms like sneezing, nasal rubbing, rhinorrhea, lacrimation and the late phase response primarily exhibiting nasal congestion/obstruction and less frequently cough [1]. Rhinitis can be classified as seasonal or perennial depending upon whether the symptoms occur in response to seasonal allergen exposure or round the year, respectively. Common seasonal allergens are derived from pollens of trees, grasses and weeds while perennial allergens are derived from dust mites, molds, animal danders and other sources of occupational origin. Often patients with perennial rhinitis show exacerbations of their symptoms on seasonal pollen exposure [2].

Elucidating the pathophysiology of rhinitis has helped immensely in its pharmacotherapy. In the sensitive individual, exposure to allergen initiates cascade of biochemical and cellular events resulting in synthesis and release of IgE. Subsequent allergen exposure leads to mast cell degranulation causing release of mediators including histamine, tryptase, cysteinyl leukotrienes (CysLT), cytokines (IL-4, IL-5, TNF-α etc.), platelet-activating factor (PAF) and prostaglandins [3]. The late phase response is primarily a cellular event involving a rush of eosinophils, basophils and lymphocytes which in turn become activated and release their mediators promoting nasal congestion, local edema and tissue damage. Pharmacotherapy of rhinitis is multivariate due to the fact that variety of interactive pathways at the base of this disease needs to be targeted. Currently, antihistamines, corticosteroids, mast cell stabilizers, decongestants, anti-leukotrienes and anticholinergics are being successfully used to treat different symptoms of rhinitis.

Due to the complexities of molecular/cellular pathways involved in rhinitis and its differential species symptomatology, it is difficult to model the disease in the laboratory animals. Guinea pigs are usually preferred for studying rhinitis because they mimic human rhinitis, although rats also seem to exhibit rhinitis symptoms on their topical sensitization with allergen [4]. Nabe et al. developed a model of allergic rhinitis using Japanese cedar pollens as a natural allergen and assessed classical H_1-receptor antagonists in passively and actively sensitized guinea pigs [5,6]. Different mediation mechanisms can be attributed to different symptoms in rhinitis model e.g. thromboxane A_2 and peptide leukotrienes in early and late phase nasal blockage [7], histamine H_1 receptors in sneezing and itching [8], histaminergic and cholinergic mechanisms in nasal secretion [9] and tachykinins in sneezing [10]. The molecular mechanisms in animal model of rhinitis or human rhinitis and the parallels between the two are incompletely understood, however, some symptoms of rhinitis such as sneezing, nose rubbing, nasal blockage and rhinorrhea can be modeled in experimental animals [11].

Although sensitization by topical exposure to allergens mimics the human situation more closely, study of rhinitis in animal model by this approach takes time to obtain an appropriate response [12]. In contrast, a prominent response is observed after systemic antigen exposure [4]. Systemic administration of antigen may accelerate the onset of disease in animals.

In the present study, we assessed different variables in ovalbumin-induced rhinitis like dose of ovalbumin, its route of administration or repeated challenge and related other parameters. The effects of oral and topical medications-histamine H_1 receptor antagonists, steroids, mast cell stabilizer, leukotriene antagonist, prostaglandin inhibitor, anticholinergic and nasal decongestant were also studied. The results indicate that the model is symptomatically and pathologically relevant to human rhinitis. It is possible to study modulation of individual disease symptoms in this model to predict the usefulness of new treatments in human rhinitis.

2. Materials and methods

2.1. Animals

Male and female Dunkin Hartley guinea pigs used for the study were provided by Animal Facility of Sun Pharma Advanced Research Company Limited (SPARCL), India. The animals weighed 250–300 g during the sensitization period (age: 4–6 weeks) and 400–450 g at the time of experiments. Animals were group housed (3 animal/cage) in an air-conditioned room at an ambient temperature of 23 ± 2 °C, 55 ± 5% relative humidity and room air changes >12/h. The room was maintained with automatic 12 h light/dark cycles, lights on at 7.00 a.m. Animals were provided with a standard laboratory diet (Harland Teklad, UK) and water *ad libitum*. All experiments were performed in accordance with the guidelines of Institutional Animal Ethics Committee of SPARCL.

2.2. Materials

Ovalbumin (chicken egg, Grade V) was purchased from Sigma, St. Louis, USA. Aluminium hydroxide and carboxymethylcellulose were purchased from S.D. Fine Chem Limited and Hi-media Laboratories, respectively. Cetirizine 2HCl, desloratadine, mizolastine HCl, fexofenadine HCl, epinastine HCl, rupatadine HCl, dexamethasone, prednisolone acetate, montelukast sodium and indomethacin were provided by the Organic Synthesis Department of SPARCL. Ovalbumin was dissolved in saline, cetirizine 2HCl was dissolved in distilled water and all other drugs were suspended in 5 mg/ml carboxymethylcellulose at the time of administration. Following drugs were formulated at SPARCL for their topical administrations: azelastine HCl, olopatadine HCl, fluticasone propionate and sodium cromoglycate. Oxymetazoline HCl (Nasivion®, Merck Ltd, India) and ipratropium bromide (Ipramist®, German Remedies Ltd, India) were obtained as marketed preparations. All the formulations were used in their original strengths.

2.3. Sensitization protocol

A procedure for active sensitization as described by Underwood et al. [13] was used with some modifications. Guinea pigs were randomized and made into different groups and sensitized on days 1, 7, 14 and 21 by intraperitoneal injection of ovalbumin (100 μg/animal) and aluminium hydroxide (5 mg/animal) dissolved and suspended, respectively in 0.9% saline solution. Nonsensitized animals received suspension of aluminium hydroxide in saline. After 7 days of systemic