CHAPTER 2

REVIEW OF RELATED LITERATURES

DEFINITIONS

Rhinitis is defined as an inflammation of the lining of the nose, characterized by one or more of the following symptoms: nasal congestion, rhinorrhoea, sneezing and occasional itching. The term' rhinitis' covers a heterogenous group of disorders which have a similar symptomology but a varied etiology. Viral and bacterial infections remain the commonest cause of rhinitis, but the prevalence of non-infectious rhinitis is increasing around the world.

Perennial rhinitis (PR) is a chronic rhinitis occurring throughout the year which is unrelated to infections, intranasal structural abnormalities, hormones and drug-induced reactions. It can be divided into perennial allergic rhinitis (PAR) and perennial non-allergic rhinitis (PNAR). These two entities have very similar clinical presentation and can be differentiated theoretically only by allergy testing. PNAR is diagnosed confidently if there is a lack of an allergic (type I hypersensitivity) etiology. In clinical practice, PR is usually diagnosed by history taking and physical examination. Perennial allergic rhinitis is triggered by allergic stimuli. The common allergens are house-dust mite, cockroach, kapok, pollens, animal danders, cat, dog. Usually on nasal examination alone, it cannot be differentiated from perennial non-allergic rhinitis. If there is co-existing diseases such as bronchial asthma, dermatitis, or conjunctivitis then PAR is more favorably diagnosed. Perennial non-allergic rhinitis is triggered by non-specific stimuli such as

cold and dry air, perfumes, strong odors, smoke, changes in atmospheric conditions and so on.

Symptoms of PR have variable effects on the patients' health, ranging from a minor irritation to a significant morbidity with loss of time from work and school. It can significantly affect the quality of patients' lives by causing disruptions in work and school attendance. Sleep patterns may be disturbed and cause an associated impairment of normal mental functioning and the ability to concentrate. The symptoms of rhinitis quickly bring patients to the attention of their physicians, particularly if secondary medical complications such as nasal polyps, rhinosinusitis or otitis media also develop.

EPIDEMIOLOGY

PR is a very common nasal disorder around the world. The prevalence of perennial rhinitis has not been directly studied . There were a few studies about the prevalence of PNAR, but that of allergic rhinitis has been widely studied around the world. The prevalence of allergic rhinitis are very common, ranging from 9-27.6%.[17] A study in London by Sibbald et al showed that adults, 16-65 years, indicated a prevalence of allergic rhinitis at 16%, being perennial 8%.[18] Studies using allergy and otolaryngology clinic patient populations with chronic rhinitis report a 28-60% prevalence of perennial non-allergic rhinitis.[19] The prevalence of perennial rhinitis in Thailand has not been studied but that of allergic rhinitis was found to be about 20.68% of Thai populations, being 22.78% in the adults.[1] Among allergic rhinitis, perennial type was found to be more prevalent than seasonal type, estimated to be 72%.[2]

PATHOGENESIS OF PERENNIAL RHINITIS

The pathophysiology of rhinitis is characterized by vascular engorgement and mucous edema. Perennial rhinitis may be caused by an allergic response or by the vasomotor reaction to cholinergic hyperactivity. The differential diagnosis of these etiologic forms poses a difficult problem for clinicians. The pathogenesis of PR and PNAR differs but both of them have hyperreactivity disorder.

Perennial allergic rhinitis (PAR) is initiated by an IgE-mediated hypersensitivity to foreign substances, i.e.allergens. To cause rhinitis, an airborne allergen must contact the respiratory mucosa. Increased amounts of allergen in the ambient air correlate well with rhinitis symptoms. Particle size of pollens, some moulds and their larger fragments (2 to 60 microns) are deposited on the nasal mucosa. In addition, pollen antigens can be detected in particle-free fractions of air. These water-soluble antigens make contact with both upper and lower respiratory tract mucosa and lead to the formation of specific IgE antibody in susceptible hosts. Clinically, allergic rhinitis is manifested by nasal congestion, rhinorrhoea, episodes of repetitive sneezing, and itching of eyes, nose and palate. It involves an early phase, largely mediated through mast cells, and a late phase which involves cellular infiltration and mediator release. In the early phase, mast cells release mediators, histamines. This results in an accumulation of histamine which gives rise to the characteristic nasal symptoms. The late phase of the allergic response (hours after challenge) involves infiltration of the nasal epithelium by eosinophils, basophils, monocytes and T-lymphocytes, which release leukotrienes, kinins, histamine and a host of other mediators. The most important part of the late-phase response is probably mediated via the production of cytokines by mast cells, TH2 lymphocytes or epithelial cells. The infiltration of tissues by cells normally present only in the blood is brought about by the production of adhesion molecules, such as VCAM-1 and E-selectin, which cause circulating eosinophils, basophils and T-lymphocytes to adhere to endothelial cells before moving through the endothelium into the tissue (diapedesis).

Neuronal reflexes also play a role in the allergic response, both by mediating local responses to mediators and possibly playing a part in the activation of T-lymphocytes.

Perennial non-allergic rhinitis can be divided into perennial non-allergic non-eosinophilic rhinitis (vasomotor rhinitis, VMR) and non-allergic rhinitis with eosinophilic syndrome (NARES). The pathogenesis of these two entities are still unclear. The symptoms might be due to increased parasympathetic activity to the nose with the release of vaso-secretory active substances. Experimental data from the cat suggest that the postganglionic parasympathetic mediator of nasal secretion is cholinergic, whereas the vascular responses appears to be due to a different mechanism. Apart from a rich sympathetic and parasympathetic innervation of the nasal mucosa there are other nerve fibres containing substance-P (SP) and vasoactive intestinal polypeptide (VIP). The secreto-vasomotor responses can be influenced by activation of these fibres and the atropine resistant vasodilatation seen following Vidian nerve stimulation thus may partly be due to activation and release of SP and VIP. Furthermore, other vasoactive substances released such as e.g. SRS or Kallikrein may participate in these reactions.[20] However, Smith et al[21] found that the IgG1 and IgG4 autoantibodies to IgE in patients with PNAR significantly higher than in the non-rhinitis group. The existence of IgG autoantibodies to IgE in non-allergic rhinitis suggests a possible role for these antibodies in the disease process, particularly in patients whose symptoms are not due to an allergic trigger. Recent studies have indicated that cold dry air induced rhinitis may also occur as a consequence of the release of mast cell associated mediators involving a non-IgE-dependent mechanism. It is possible that mast cell activation occurs as a consequence of changes in osmolality of nasal secretions following provocation.

TREATMENT OF PERENNIAL RHINITIS

The management of patients with perennial rhinitis consists of

1. Environmental control by avoiding the allergens and irritants.

For PAR, patients should be advised on how to minimize their exposure to allergen, especially house-dust mite.

2. Pharmacotherapy

For PAR with intermittent symptoms, an oral H1-antihistamine and an occasional oral decongestant can be used. For persistent symptoms, a topical nasal steroid is advised,[12] possibly supplemented with an antihistamine.

For non-allergic rhinitis with intermittent symptoms, topical or oral decongestants can be used. Topical ipratropium bromide is useful for drying up watery rhinorrhea. For moderate symptoms, either a topical nasal steroid or topical ipratropium bromide should be used.[11]

3. Immunotherapy.

This treatment may provide significant benefit to patients with allergic rhinitis who do not respond to environmental avoidance measures and medications and is preserved only for those with perennial allergic rhinitis who have poor response to pharmacotherapy.

TOPICAL NASAL GLUCOCORTICOSTEROID IN PERENNIAL RHINITIS

For more than two decades, steroids have been proved to be effective in the treatment of allergic rhinitis.[22] In therapeutic dosage, systemic steroids produce unacceptable side-effects,[23] suppressing the hypothalamo-pituitary-adrenal axis (HPA)[24]

and therefore cannot be recommended for prolonged usage in seasonal allergic rhinitis and perennial rhinitis. The topical application of recently developed steroid aerosols is of great advantage in the treatment of non-infective rhinitis.[8,25,26] The modern steroid aerosols are inactivated after the first passage in the liver, following resorption by the respiratory or gastrointestinal mucosa. The desired therapeutic effect is therefore, restricted to the mucous membrane, and the well-known undesirable general side effects of the steroid hormone are avoided. The main indications for nasal application of steroid aerosols are allergic rhinitis, non-allergic rhinitis and polyposis nasi. These medications have allowed many patients to achieve control of their rhinitis symptoms with enhanced compliance, particularly with some of the preparations with newer once-a-day dosing schedules. Various preparations are available, including intranasal beclomethasone, flunisolide, budesonide, triamcinolone and fluticasone. They can provide significant relief of symptoms of allergic rhinitis and also relieve symptoms of perennial nonallergic rhinitis. Many clinical investigators agree that the main clinical benefits of nasal glucocorticoids are due to their ability to reduce nasal mucosal inflammation. Multiple anti-inflammatory actions have been demonstrated. Nasal glucocorticoids effectively reduce mucosal swelling and secretions by decreasing the number of basophils, mast cells, eosinophils and neutrophils, as well as the amounts of mediators in the nasal mucosa and nasal secretions. They can inhibit both early and late responses to inhaled antigen and decrease nonspecific hyperreactivity of the nasal mucosa during the early response to nasal provocation with antigen. Generally, significant benefit is seen within the first 7 days. The most common side effects of nasal glucocorticoid sprays are nasal irritation and stinging, which can usually be prevented by aiming the spray slightly away from the nasal septum. Epistaxis and hemorrhagic crusting of the nasal septum can also be reduced by this maneuver; applying a small amount of petroleum jelly or other lubricant gel to the nasal septum before inserting and inhaling the spray will usually prevent these problems. Irritation of the pharynx may occasionally occur with nasal corticosteroids. Nasal septal perforation has been reported rarely.[27] Intranasal glucocorticoids are rapidly degraded enzymatically in the

nasal mucosa to less active metabolites. Any unchanged drug, that is absorbed, is metabolized in the first pass through the liver. Suppression of the hypothalamic-pituitary-adrenal axis has not been a significant clinical problem. In perennial non-allergic rhinitis topical corticosteroid reduced reactivity to methacholine, acetylcholine analog, in a dose-dependent manner, suggesting a relationship between nasal glandular hyperreactivity and mucosal inflammation.[5]

BUDESONIDE

Budesonide is a non-halogenated glucocorticosteroid (GCS), which has been developed to provide a potent, local, anti-inflammatory action and subsequently to undergo rapid systemic metabolism to products of low GCS activity, thereby maximizing patient tolerability. It was introduced in 1979 with an improved pharmacokinetic profile provided a further useful treatment in perennial rhinitis. It is highly metabolized in the liver with negligible local metabolism in the nasal cavities and is eliminated more rapidly than similar halogenated steroids. Budesonide has been proved to be efficacious both in perennial allergic and non-allergic rhinitis with no evidence of tachyphylaxis even after long periods of use.[3,4,5,6,13,16,28] Comparing with other topical steroids using for perennial allergic and non-allergic rhinitis, budesonide was found to be superior or at least similar to other modern topical nasal steroids.[8,29] The high glucocorticosteroid-receptor affinity of budesonide, coupled with adequate water solubility, confers a topical potency and an anti-rhinitic efficacy that have not been exceeded by other therapeutic agents in comparative clinical trials.

As studied by dose-related efficacy, clinical studies have shown that the therapeutic effects of budesonide increase as the dose increases up to 400 micrograms daily. Balle[4], Pedersen et al[15] and Irander et al[30] showed that budesonide 400 micrograms per day was more efficacious than 200 micrograms per day. Wight et al[3]

and Pedersen et al[31] found that budesonide dry powder 400 micrograms daily could relieve the symptoms of allergic rhinitis as effectively as 800 micrograms daily, confirming that 400 micrograms per day is the optimal budesonide dosage for reliable symptom relief and good tolerability. Nevertheless these studies were done in the Caucasians whose nasal cavities are much larger than the Orientals'.

Budesonide aqueous nasal spray is a very safe drug. At the usual dosage of 400 micrograms daily, side effects rarely occur. If it occurs, it is well tolerated with mild adverse effects usually confined to nasal irritation causing sneezing immediately after use, nasal dryness, crusting, localized stinging, itching, nasal secretion and epistaxis, Sneezing appears to be caused by the propellants used in the pressurised nasal spray, but not in the aqueous form. No histopathologic changes in the nasal mucosa were detected in 24 patients with perennial rhinitis treated intranasally with budesonide 200 to 400 micrograms daily for periods of up to 5.5 years.[32] Wight et al[3] found that basal and stimulated plasma cortisol levels remained unchanged with either dose of budesonide and no increase in adverse effects occurred with higher dose therapy.