CHAPTER 2

REVIEW OF RELATED LITERATURES

EPIDEMIOLOGY

Allergic rhinitis is usually a mild disease, however, it can make patients uncomfortable and interfere with their sleeping, eating and lifestyles. Afflicted individuals often develop secondary effects such as sinus infections, otitis media and nasal polyp formation (2).

About 5%-10% of the general population which may have allergic rhinitis symptoms, however, only 2-4% are suffering from the disease with daily symptoms and need for a medications (4). Therefore, more recent studies are primarily concerned with asthma and data on allergic rhinitis are only secondary (2). Allergic rhinitis occurs often in patients with other allergic diseases: 80% of children presenting with asthma and 50% with atopic dermatitis. Data from studies done differently are difficult to be compared. However, it seems almost certain that there has been an increase in the occurrence of allergic rhinitis and asthma in industrialized nations.

In a population study among children less than 14 years in one village in Indonesia (1989), it was found that

the prevalence of atopic disease was 25.5%, consisting of 8.2% cases of bronchial asthma, 10,2% allergic rhinitis, 4,9% atopic dermatitis and 4.5% urticaria (11).

THE ROLE OF HISTAMINE IN THE PATHOGENESIS OF ALLERGIC RHINITIS SYMPTOMS

Histamine, especially the H_1-receptor, is the major pharmacologic agent associated with acute allergic reactions that result from IgE dependent from mast cells and basophils, which can cause all of the pathologic features of allergic rhinitis (see appendix 1) (12,13). Widespread biologic activities of histamine are mediated through activation of specific cells surface receptors (12). Most of the important histamine effects in allergic diseases are mediated through the H_1-receptor. These include smooth muscle contraction, increase vascular permeability, pruritus, prostaglandin generation and activation of vagal reflex. Histamine - induced vascular permeability is an H_1-mediated effect that is caused by contraction of actinomycin fibers in endothelial cells of the post capillary venules. Increased permeability occurs in all allergic diseases and therefore is a feature of allergic rhinitis. Histamine is also the only proven mediator of pruritus of allergic rhinitis symptoms which result in sneezing attack. In the nose the glandular component is indirectly mediated by histamine through a vagal reflex (12).

Insufflation of specific allergen into the nose of a person with allergic rhinitis induces congestion, pruritus, sneezing and nasal hypersecretion. Examination of the putative mediators reveals that histamine can cause all of the pathologic features of allergic rhinitis and there were excellent response of anti histamine experienced by most of allergic rhinitis patients. Other mediators such as kinin, prostaglandin and leucotrien contribute to allergic rhinitis symptoms, however, histamine is the primary mediator of this disease (13).

ANTIHISTAMINE

Antihistamine, especially H_1-receptor antagonist have been widely used in clinical medicine since 1940 and in 1970, antihistamines with a gastric anti secretory effect have been developed. These are now subclassified as H_2-receptor antagonist. H_1-receptor antagonists bear some structural resemblance to histamine. It contains an ethylene group. The traditional classification of histamine H_1-receptor antagonist is according to chemical structure (see table 1), however the new generation of antihistamine does not fit into the old classification system (14).

Table 1. Classification of antihistamine according to the chemical structure (6)

CHEMICAl CLASS	GENERIC NAME
1. Ethanolamine	Clemastine Diphenhydramine
2. Ethylenediamine	Tripenilamine
3. Alkylamine	Chlorpheniramine Tripolidine Acrivastine*
4. Piperazine	Hydroxyzine Cetirizine*
5. Phenothiazine	Promethazine
6. Piperidine	Astemizole* Cyproheptadine Ketotifene Loratadine* Terfenadine*

* Newer, second generation antihistamine, usually less sedating

H_1-antihistamines are well absorbed when administered by mouth and the peak serum concentrations reaches approximately 2 hours after administration and symptom relief begins within 30 minutes. The maximal antihistaminic effects occur several hours after peak serum concentration have passed and persisted even when serum concentration of the parent compound have declined to the lowest detectable limit (14). Therefore H_1-receptor antagonist should be given before an anticipated allergic reaction, in order to achieve maximal efficacy.

All antihistamines, regardless of the class provide an effective antihistaminic action in vitro or in vivo and against histamine skin wheals & flare reactions in human, however, differences in potency do exist among the compounds. Some of the first generation H_1-receptor antagonists such as Tripenilamine and Tripolidine in recommended doses are not very potent in suppressing wheals and flare. The others, such as Chlorpheniramine and Hydroxyzine are relatively potent and should not be discarded from the therapeutic use (13).

The most common adverse effects of classic antihistamines are physiologic depression or suppression. In some instances depending on the dose, classic antihistamine produce sedation, impair psychomotor performance and potentiate the effects of other Central Nervous System (C.N.S.) depressant. The explanation for the C.N.S. effects is because classic antihistamines are composed of multiple aromatic or heterocyclic rings and alkyl substitute in the antagonists result in their being lipophilic (small water-soluble). A lipophilic antihistamine that circulate in an unchanged form unbound to protein enter the brain relatively easily (6).

The sedation effect of classic antihistamines were found at 2 to 4 hours after administration of the drug. Frequently, this adverse effect is dose related and correlates

with high serum drug concentrations. Alkylamine causes mild sedation compared to Ethylene diamine which gives a moderate sedation, while Ethanolamine and Phenothiazine give a marked sedation (6,15).

All of the classic antihistamines and most of the second generation antihistamines currently available are metabolized in the liver, except Cetirizine of which 70% is excreted unchanged within 72 hours in the urine. Clearance rates and serum elimination half life values are extremely variable (see table 2), ranging from approximately 24 hours or less for Chlorpheniramine, Brompheniramine, Hydroxyzine, Terfenadine, to 9.5 days for Astemizole and its active metabolites (14,16).

The duration of action of H_1-receptor antagonist can be assessed objectively by suppression of histamine or allergen induced wheals and flare in the skin or subjectively by suppression of symptoms for example allergic rhinitis or urticaria (14).

CHLORPHENIRAMINE

Chlorpheniramine is one of the classic H_1 - antihistamine belonging to the Alkylamine class. It is potent, highly effective and widely used antihistaminic drug with a mild sedation effect. It has been used for 30 years

with the therapeutic effect generally accepted as not greater than 4 hours (17). Presently, in Indonesia Chlorpheniramine is available either alone as standard anti allergic treatment or in combination with other drugs as cold tablet easily found in the market.

Table 2. Serum half-life of antihistamines and serum elimination half-life (hr) (16)

H_1-receptor antagonist	Serum elimination half-life (hour)	Significant wheal suppression (hour)
1. Chlorpheniramine	24.4	24
2. Brompheniramine	24.9	3-9
3. Tripolidine	2.1	-
4. Hydroxyzine	20.0	2-36
5. Cetirizine	7.4	24
6. Loratadine	11.0	24
7. Terfenadine	4.5	12-24
8. Astemizole	10 days	Weeks

Pharmacokinetics study were done by several authors.

1). Peet study (1972) found that the peak plasma level of Chlorpheniramine in man was achieved in 2 hours after administration and the plasma half-life of 3 times a day of 4 mg per oral dose was 12 -15 hours and 28 hours after a 4 mg intra venous dose (17).

2). Simons study in children (1982) was consistent with Peet at al, where the plasma half live of Chlorpheniramine was 13,1 ± 6.6 hours and the peak serum concentration occurred at 2.5 ± 1.5 hours after administration. Furthermore, the significant suppression of wheals and flare occurred for up to 24 hours (18).

3). Bantz study (1987) confirmed a relatively long serum 8 mg Chlorpheniramine half-life in adults. The half life time was 24 hours on average and the suppressive effect on histamine-induced wheals was 55% after two hours and significant for up to 24 hours. That study, however, was not designed to evaluate the efficacy of Chlorpheniramine in terms of relieving symptoms of allergic rhinitis (5).

4). Another Simons study (1990) evaluated the efficacy of 4 mg Chlorpheniramine in terms of suppression of histam ine-induced wheals and flares compared to a new anti-histamine and to placebo. It was found that Chlorpheniramine had a maximum suppressive effect on histamine-induced wheals of 35 % ± 28% for up to 12 hours. Since it was a single dose study, however, it did not reflect dynamic repetitive maintenance dosing with varying rates of absorption, receptor affinities and rates of metabolic clearance (10).

There were several clinical trials to evaluate the efficacy of Chlorpheniramine in terms of relieving symptoms of allergic rhinitis.

1). Study of Kemp at al (1985) evaluated the efficacy of 4 mg Chlorpheniramine three times a day compared to 60 mg Terfenadine twice a day and to a placebo. The result showed that the overall effectiveness of Chlorpheniramine group and Terfenadine were equivalent and significantly better than that of the placebo with 59.7% of the Chlorpheniramine and 60.2% of the Terfenadine patients giving a moderate and complete relief of symptoms as compared with only 30.1% of the placebo patients. Furthermore the evaluation of safety was based on the experience of reported adverse effects throughout the study. Sedation effect was significantly higher in Chlorpheniramine group (18.8%) than that in the Placebo where it was reported by only 2.4% patients (8).

2). Contrary with the Kemp study, other clinical trial of Weiler's (1988) which evaluated four times a day of 4 mg Chlorpheniramine compared to Azelastine and to a Placebo. The result of the study showed that Chlorpheniramine group did not show any significant difference in symptom improvement compared to the placebo. While sedation effect was reported in 52% and 25% of the Chlorpheniramine and the placebo groups respectively (9)

CETIRIZINE

Cetirizine is a major human metabolite of Hydroxyzine but it is significantly less sedating than the parent compound and other classic antihistamines (3,19). In addition to its H_1 - antagonist effect, Cetirizine has an anti inflammatory effect associated with decreased eosinophil infiltration to the site of allergic reaction. This may enhance its usefulness in perennial allergic rhinitis treatment where the nasal mucosa is in a constant state of inflammation (3,19,20). The half -life time of Cetirizine is 7 hours and the maximal suppressive effect on histamine -induced wheals is more than 80% for up to 24 hours (10). From the Mansmann study, Cetirizine (10 mg) once daily was effective and well tolerated for relieving symptoms of perennial allergic rhinitis. In this study a good response (more than 50% symptoms improvement) occurred in 62% of cases, which was significantly more than in the placebo group (the good response was 25%). The sedative adverse effect was not significantly different from the placebo (15% : 16%) (7).