CHAPTER 3

RESEARCH METHODOLOGY

RESEARCH QUESTIONS

Primary question

Is there any difference in the success result of relieving symptoms between 8 mg Chlorpheniramine and 10 mg Cetirizine once daily doses in the treatment of perennial allergic rhinitis patients ?

Secondary question

When the drugs are given as once daily dose at bedtime is there any difference of adverse effects between 8 mg Chlorpheniramine and 10 mg Cetirizine, especially sedation effect at day time during the treatment of perennial allergic rhinitis patients ?

Which one is more cost effective, 8 mg Chlorpheniramine or 10 mg Cetirizine in the treatment of perennial allergic rhinitis ?

HYPOTHESIS

There is no difference of the success result between 8 mg Chlorpheniramine once daily dose given at night (P_1) and 10 mg Cetirizine once a day (P_2) in terms of relieving

perennial allergic rhinitis symptoms.

There is no difference of adverse effects between 8 mg Chlorpheniramine and 10 mg Cetirizine given as once daily dose at night during the treatment of perennial allergic rhinitis patients.

ASSUMPTIONS

1. Patients were allocated completely at random in two sequences of treatment, if there was influence of the period effect it would be distributed in the two groups at random.

2. A washout time of 4 days was adequate, because recommended washout period was three times of the half-life of the drug in studied at least. The half-life of Chlorpheniramine and Cetirizine have been confirmed were 21-25 hours and 7 hours respectively.

RESEARCH DESIGN

STUDY DESIGN

The study design was double-blind, randomized, cross-over clinical trial (the overview see appendix 2). The study evaluated the clinical efficacy of Chlorpheniramine (8 mg once daily doses at bedtime) in terms of relieving symptoms of perennial allergic rhinitis patients compared to Cetirizine

(10 mg). Eligible patients who fulfilled the inclusion and exclusion criteria were blocked randomized by 10 and cross-over in two sequences of treatment. The first was Chlorpheniramine (8 mg) followed by Cetirizine (10 mg) and the other was in the reverse order. There was a washout period between the two treatments. The effectiveness of the treatment evaluated in the study was in terms of relieving symptoms of perennial allergic rhinitis by patient's subjective assessment using a symptom rating scale and physical examinations using a sign rating scale. Adverse effect of the drugs in term of anticholinergic activity and sedation effect were blindly evaluated by patient assessment, while the severity of sedation effect was evaluated subjectively using Stanford sleepiness scale.

DESIGN JUSTIFICATION

1. Clinical trial was needed because the aim of the study was to evaluate the efficacy of 8 mg Chlorpheniramine in terms of relieving symptoms and to see its adverse effect in the treatment of perennial allergic rhinitis patients.
2. Randomized control studies would avoid selection bias and allocation bias and to make a balance between the two groups; so that the measured or unknown prognostic factors and other characteristic of the subject at the time of randomization would be on the average or balanced

between the two sequences. The statistical test assumed randomization for validity of the interpretation (21). Block randomization was used in order to achieve balance over time in the number of subjects who were randomized to each sequence.

3. Double - blind would avoid an expectation and assessment bias, from both the researcher and the patients.
4. Crossover design in this study is appropriate because:
   4.1. Perennial allergic rhinitis is a chronic and not life- threatening disease.
   4.2. The treatment is directed to symptomatic relief, so the disease still exist.
   4.3. The effect of the treatment (antihistamine) can be measured after a short time after administration.
   4.4. Serum half-life time of the two drugs studied are already established (7 - 25 H). So the wash-out period is assumed to be at least 3 days (22).

Additionally, the clinical efficacy in terms of mean skin tests percent suppression and Chlorpheniramine level are progressively decreased and returned to baseline after 72 hours.

5. Crossover design will give a complete matching because the subjects become the control of themselves. The design will increase the precision of the comparison among the

treatment and control confounding factors between the subjects.

The outcome variables were symptoms of the disease which were frequently experienced by the patients at night and early morning so most of the outcome could not be seen by the researcher. To overcome that issue patients had to record their symptoms themselves by using symptoms diary card.

The important factor which might be influencing the symptoms of perennial allergic rhinitis was the concentration of allergen exposure which might be seen from the severity of symptoms. Therefore, patients were grouped according to the severity of symptoms into moderate (the score were 2) and severe groups (the score were 3). Then each group was randomized and allocated in two sequences of treatment.

TARGET POPULATION

The target population of this study were all of the out patients who were diagnosed to have perennial allergic rhinitis at the Ear, Nose and Throat department of Kariadi hospital. The age of the subject was 16 to 55 years. Both males and females were eligible.

SELECTION CRITERIA

INCLUSION CRITERIA

Following patients were included in this study : :

1. Patients with a diagnosis of perennial allergic rhinitis with a history of serial sneezing attacks, watery nasal secretions, nasal blockage and physical examination of pale, bluish edematous nasal mucosa, with serous nasal secretions.
2. Patients who gave positive skin prick testing reaction to at least one of the perennial allergens such as dust-mite, house dust, and animal dander (cat, dog, chicken). Skin tests were positive when the wheal was equal to or larger than the wheal of histamine control.
3. Patients who had symptoms for at least two days before entry into the study and rhinitis symptoms severity score of 2 or more.
4. Those who have normal liver and renal function tests because Chlorpheniramine was metabolized in the liver and Cetirizine was excreted by the urine.
5. Patients with the duration of the disease (allergic rhinitis) was at least three months before the study begins.
6. Patients did not used antihistamines at least within 4 days before entry into the study (except Astemizole 4 weeks).

7. Those who have no nasal infections (thick and colored nasal secretions with large number of neutrophil was observed).

EXCLUSION CRITERIA

Patients who had the following conditions were excluded from the study .

1. Pregnant and lactating women (20). Although teratogenic effects and fetal anomalies in human have not been proven, the effect had been noted in animals. H_1-receptor antagonist should therefore be used with caution during pregnancy. H_1-receptor antagonist secreted in breast milk was comparable in serum level.
2. Patients who had history of active asthma attack because anticholinergic effects can make patients' bronchial secretions thick.
3. Patients using corticosteroid before study. The drug should be stopped one week before study because corticosteroid has an antiallergic effect.
4. Patients who receive hyposensitization within one year, because a maximal effect of hyposensitization would be achieved within six months.
5. Patients with complications of nasal polyps.
6. Patients who have symptoms of sinusitis, when there were thick post nasal drainage, low grade of facial pressure and headache. Paranasal sinus X-Ray was performed. The

patients whose paranasal sinus X-Ray shown air fluid level or sinus mucosa lining of more than 5 mm would be excluded from the study.

7. History of glaucoma, especially narrow angle type because anticholinergic effect would influence the symptoms.
8. History of prostate hypertrophy, because anticholinergic effect might adversely produce urinary problems.
9. Patients with severe nasal septal deviation.

SAMPLE SIZE

The sample size of the study was calculated from the primary research question. The formula used in the study was a sample size calculation for comparing two binomial proportion of paired sample case.

$$n = \frac{[\ Z_{1-\alpha/2} + 2\ Z_{1-\beta} \sqrt{(p_A\ q_A)}\ ]^2}{4\ (\ p_A - 0.5)^2\ p_D} \text{ matched pairs} \quad (23)$$

p_D = projected proportion of discordant pairs among all pairs

p_A = projected proportion of discordant pairs of type A among discordant pairs

There was no information about the proportion of responses of Cetirizine and Chlorpheniramine in the matched-pair design clinical trial. A pilot study has been done for getting the value of p_D. According to the efficacy study in terms of suppressive effect of histamine-induced wheals and

flares, both Cetirizine and Chlorpheniramine were significant for up to 24 hours, but there was a difference in the maximum of suppressive effect of histamine-induced wheals and the price. Cetirizine has maximum suppressive effect of more than 80% while Chlorpheniramine has suppressive effect of 55%, but the price of Cetirizine was about 10 times more expensive. Regarding to those factors, an equivalent difference of 0.25 was acceptable. So in matched-pairs where there were differences in response, about 3/4 of the pairs Cetirizine responded, while Chlorpheniramine did not. And in 1/4 of the pairs, Chlorpheniramine responded, but Cetirizine did not. It means that the projected proportion of discordant pairs of type A among discordant pairs was : $p_A = 0.75$ and $q_A = 0.25$ The layout of data of the pilot study is in table 3.

Table 3. Lay out data of the pilot study

		10mg CETIRIZINE		
		Success	Failure	Total
8mg CHLORPHENIRAMINE	Success	7	2	9
	Failure	4	3	7
	Total	11	5	16

In the pilot study, 20 patients were randomly allocated in two sequences of treatment. Of these patients, 16 finished the treatment schedule, four of them dropped out

at the first period of treatment. Similar responses (success and failure) were obtained in 10 persons (0.62). So the p_D value was 1- 0.62 = 0.38 ---> round up to 0.40. The sample size was calculated according to the significance level of 0.10 and power of 0.90.

$Z_{1-\alpha}$ = 1.645 (two- tail) p_D = 0.40

$Z1-_{\beta}$ = 1.28 p_A = 0.75

$$n = \frac{[\ 1.645 + 2 \times 1.28 \times \sqrt{(0.75 \times 0.25)}\ ]^2}{4 \times (0.75 - 0.5)^2 \times 0.40}$$

= 75 matched pairs

Inflated for dropouts 20% --> 90 cases.

INTERVENTION

Patients who fulfilled the eligibility criteria were enrolled in the study. Patients were grouped based on the patient's symptoms score into the moderate group (symptom score of 2) and the severe group (symptom score of 3). Using random numbers, patients of each group was block randomized and allocated in two sequences of treatment. The first sequence received 10 mg Cetirizine for 7 days, followed by a washout period of 4 days and continued by Chlorpheniramine (8 mg) for another 7 days. The other sequence was in the reverse order.

To minimize sedation effect at day time during 8 mg Chlorpheniramine treatment and for maintaining the double blind design, either Cetirizine or Chlorpheniramine were given in an identical opaque capsules as once daily dose at night (7.00 p.m). Throughout the study, participants were not allowed to take any other medications besides the medications that were administered in the study protocol. The duration of each period of treatment was 7 days, because the pharmacokinetics study, both Cetirizine and Chlorpheniramine achieved a steady state by the third dose (5,7).

WASH-OUT PERIOD

Wash-out period is a period between treatment days in the trial, during which the effect of the treatment given previously is believed to disappear. So it is assumed that all measurement taken after the washout period are no longer affected by the previous treatment. It is also assumed that there will be no more carry - over effect. The minimum recommended washout time period is three times of the half-life of the drug studied (22). Because the longest half-life time of Chlorpheniramine was 25 hours, so three times of 25 hours is 75 hours. Hence the wash out time of 4 days is long enough. No drug was given during the washout period.

COMPLIANCE, CONTAMINATION AND CO-INTERVENTION

COMPLIANCE

To maintain the compliance, patients were explained about the aim of the study and the benefit of the selection of appropriate antihistamine treatment for their rhinitis in the future. Only those people likely to follow the study protocol were enrolled in the study. People who lived too far away from the hospital and who were likely to move before the scheduled termination were not included in the study. The drugs were given as once daily dose, so it is easy to be complied.

For evaluating the compliance, patients were given a medication bottle with sufficient number of Cetirizine or Chlorpheniramine (in the identical capsules) to complete their therapy. Patients were instructed to ingest one capsule every night and to return the bottle and remaining capsules after each phase of study for capsule counting.

CONTAMINATION

The drugs (Chlorpheniramine and Cetirizine) were presented in an identical opaque capsule and put it in a bottle. Each bottle was given a code number which was consist of random number, sequence code and period number. The drug was given to the patient for each period of treatment, so the

drug for the second period was given after they finish taking the drug of first period, when they came for control visit. So contamination between the two drug can be avoided.

CO-INTERVENTION

For avoiding co-intervention, investigators stayed in close contact with the subjects. Between scheduled visits patients were free to come to the hospital/ clinic or phone the researcher at any time the symptoms cannot be tolerated. The researcher considered whether this patient needed a rescue medication or not. The rescue medication would be given for treating the emergency cases and recorded in the diary symptoms card. A home visit was performed when the patient was unable to come on the visit day.

OPERATIONAL DEFINITION

1. Perennial allergic rhinitis is a chronic rhinitis which is characterized by sneezing attack, nasal secretions and nasal obstruction with a pale, bluish edematous nasal turbinates and clear nasal secretions with positive result on skin prick testing to one or more perennial allergens such as house dust, dust mite, or animal dander.

2. The result of the treatment

Antihistamine is a pharmacological treatment which is antagonize histamine at the receptor site. The effect of the treatment is relieving allergic rhinitis symptoms. Perennial allergic rhinitis patients might have symptoms at different time during 24 hours period, therefore, patients were asked to record their symptoms twice a day at night and early morning. The night score record was combined with the next morning score record, whichever was more severe was evaluated as an entity of 24 hours period of the rhinitis symptoms.

THE RESULT OF THE TREATMENT

PATIENT ASSESSMENT

All patients were explained how to use the symptom rating scale for evaluating their rhinitis symptoms and how to record it in the symptom diary card. The symptoms evaluated were emphasized on the three main nasal symptoms: sneezing attack, rhinorrhea and nasal obstruction as an entity of the rhinitis symptom. Because the symptoms of perennial allergic rhinitis often come out at night time and early morning, the symptoms were recorded every night (at 8 p.m.) and early morning (at 7 a.m) during the study days. The symptoms were subjectively measured by patients using a four point scale of Rhinitis symptoms.

Rhinitis symptom rating scale :

0 (zero): when there is no symptom

1 (mild) : when there are symptoms but these do not disturb patient's activity

2 (moderate) : when the symptoms disturb patient's activity or her/his sleep

3 (severe): when the symptoms disturb patient's activity and her/his sleep.

The result of the treatment was divided in 2 groups:

1. **Success result** is when after taking the drug the symptom score changes to 0 or 1 regardless of whether the previous score 2 or 3 in at least 5 of the 7 days treatment.

2. **Failure result** is when the symptom score changes to 2 or 3, or no changes from symptom score of 2 or 3 in at least 3 of the 7 days treatment.

PHYSICIAN ASSESSMENT

Perennial allergic rhinitis might present at the various clinical condition. It can vary from no sign to severe nasal mucosa edema with serous nasal secretions. For evaluating the result of the treatment objectively, physical examinations of the nose was performed on the day of the visit after 7 days of treatment. Patients were examined by two Ear,

Nose and Throat physicians independently to see the nasal conditions and whether there was a complication during the period of study. To see the inter-rater reliability between the two observers, Kappa statistic was used. Physician assessment was performed based on the physical examination findings during the visit day using 3 point sign rating scale.

Sign rating scale :

0 : when there was no edema or mild edema and no nasal secretions

1 : when there was mild/ moderate edema with a little nasal secretions

2 : when there was severe/total nasal obstruction, or profuse nasal secretions or both.

The result was defined as success when the physical findings score was 0 and the failure result was when the physical findings score was 1 or 2.

ADVERSE EFFECTS OF THE TREATMENT

Adverse effect events evaluated during the treatment were sedation and anticholinergic activity such as dry mouth, fatigue, visual problem and urinary problem. Studies of antihistamine-induced drowsiness have usually relied upon indirect assessment, such as clinical impressions, questionnaire and visual motor performance. In this study

patients were asked to record any unusual sensation which were experienced throughout each period of the treatment in their symptom diary card. If there was sedation effect, the severity of day time somnolence effect in this study was measured by subjective assessment using 7 point Stanford Sleepiness Scale (24). Each number on the Stanford scale correspond to a set of phrases which qualitatively describe the subject's level of sleepiness, where the larger number on the scale was corresponding to greater sleepiness. All adverse effects, whether noted by the patient as a comment on the diary card or elicited by questioning were recorded on the case report form.

Stanford sleepiness scale:

1. Feeling active, vital alert, wide awake
2. Functioning at a high level but at not peak, able to concentrate
3. Relaxed awake but not fully alert, responsive
4. A little foggy, let down
5. Beginning to lose track, difficulty in staying awake
6. Sleepy, prefer to lie down
7. Almost in reverie, sleep onset appears imminent.

Sedation effect was defined as positive when they have Stanford sleepiness score of 3 or more in at least 2 days of the 7 days treatment.

Although a subjective assessment is less reliable compared to objective Electroencephalographic (E.E.G.) method (15), it has however a clinical meaning. Evaluation of the sedative effect with objective E.E.G. method is not practical for many of the out patients and is too expensive.

DATA COLLECTION

Using a standardized form, taking history were done by researcher and assistance researchers for getting information about data of sex, age, duration of rhinitis, severity of rhinitis symptoms, other allergic disease manifestations and the characteristic of the rhinitis symptoms. Information about the characteristic of symptoms consist of the kind of the most disturbing symptoms, the time of the worse symptoms occurred, frequency of sneezing when they have attack, frequency of nasal blowing when they have worse symptoms and other symptoms which might be found during their worse symptoms.

Physical examinations (ear,nose and throat) was performed by two E.N.T. doctors independently to see the nasal conditions to confirmed whether there were no exclusion criteria. Allergic skin testing were done using skin prick testing technique by an inhalant allergens kit. Laboratory examinations for examining the liver function, renal function

and cytologic nasal smear examination were done.

Before receiving the drug, patients were given a symptoms diary record form and they were explained how to record their symptoms during the study period. They were also asked to record adverse effects of the treatment if any, such as dry mouth, visual disturbance, urinary problem, sedation and headache. Patients were asked to measured the severity of sedation effect by themselves using Stanford sleepiness scale. All records were submitted to the researcher at the control visit day and were checked whether the patients did properly. To avoid the difficulties in the data analysis, the subjects were enrolled in the study when all of the diagnostic tests have been confirmed and the patients fulfilled all of the entry criteria.

DATA ANALYSIS

Baseline data were present as a descriptive statistics such as age, sex, severity of symptoms, duration of the disease and the variation of the perennial allergic rhinitis symptoms.

The Mc Nemar test was employed to assess the differences of outcome and adverse effects between 8 mg Chlorpheniramine and 10 mg Cetirizine treatment (25,26).

SUBGROUP ANALYSIS

In any trial of a therapeutic intervention there was a potential, that the treatment effect would vary in a different patient subgroup. Subgroup analysis was done for "explanatory external variables" such as severity of symptoms. The appropriate test was Mantel-Haenszel statistic (21).

In the trial of a therapeutic intervention there was also potential for drop-out, non compliant and confounder event. During antihistamine treatment of perennial allergic rhinitis there are possibilities that patients getting infection (viral or bacterial) which might influencing or confound the treatment results. This study followed a principle of analysis by intention to-treat. The data were analyzed in two ways, both including and then excluding dropouts, non compliant patients and patients who have a confounders event in the analysis (27).

COST EFFECTIVENESS ANALYSIS

Cost effectiveness analysis is one of the methods of assessing the cost of health treatments. This analysis is appropriate for this study since the aim of this study is comparing two treatments of meeting the same objective (relieving allergic rhinitis symptoms). If two alternative courses of action meet the objective equally well, then the

less costly would be chosen on efficiency (or cost effectiveness) ground (28).

In cost effectiveness analysis, the cost of different drug regimen to achieve a common outcome (effectiveness) was divided by its effectiveness. Threfore the result obtained was the cost per unit outcome (29).

The cost was calculated from the patient' perspective.

ETHICAL CONSIDERATION

This study may present some ethical problems. The main ethical questions would be discussed below:

INFORMED CONSENT

Written informed consent was obtained from every participating patient before entry into the study.

EVALUATION OF RISK AND BENEFIT

Some physicians might argue that Chlorpheniramine was a classic antihistamine with a conventional regimen 4 mg, 3 to 4 times a day. Was it effective in preventing morning symptoms of perennial allergic rhinitis when the drug was taken at night ? There was no study to evaluate the efficacy of a 8 mg Chlorpheniramine in terms of relieving symptoms of allergic rhinitis, however as discussed in chapter 2, there

was an evidence that Chlorpheniramine (8 mg) was effective in terms of suppression on histamine-induced wheals & flares for up to 24 hours and the half-life was about 21 to 25 hours. It was needed, therefore a scientific approach to provide the evidence of the efficacy of this drug, so that the community as a whole might get the benefit.

Some physicians might argue because of the risk of Chlopheniramine side effects especially sedative adverse effect. As discussed in chapter 2, Chlorpheniramine was an alkylamine class which has mild sedation compared to other classic antihistamines. The sedation effect correlates with the drug serum level. In this study Chlorpheniramine was given as a once daily regimen and it was given at night (7.00 p.m.). The peak serum level of antihistamine was reached at 2 to 4 hours after administration, so that the sedation effect could be occurred at 10.00-12.00 night when the patients sleep.

In Indonesia 4 mg Chlorpheniramine 3 times a day has been widely used as an antiallergic treatment in the primary health care setting and in the government hospital for decades and it has been well accepted with tolerable side effect. We believe that the only way to find out the efficacy of 8 mg Chlorpheniramine once daily in the treatment of perennial allergic rhinitis patients and whether the advantage is less

of the adverse effect, is to do a randomized control trial with a rigorous methodology.

PROTECTING THE PATIENTS

An ethics review committee reviewed and approved this study protocol before the trial. A written informed consent was obtained from all patients who entered into the study. Patients can decide freely whether or not to participate in this study. They are free withdraw from the study any time.

LIMITATION

The subject of this study included uncomplicated allergic rhinitis patients who came to the referral hospital. In Indonesia most of the allergic rhinitis patients come to the referral hospital when they really are disturbed by the severity of the allergic rhinitis symptoms or when they fail from the first medication in the primary Health Center. To solve this problem, every patient complaining rhinitis for more than three months would be examined to see the possibilities of having perennial allergic rhinitis.

Application of the results of this study in the real practice should be considered, i.e. antihistamine is a basic pharmacologic treatment besides other kind of treatment of allergic rhinitis, since allergic rhinitis patients usually

come with various conditions. In the physical examinations, physicians performed anterior rhinoscopy using nasal speculum, head lamp and ephedrine application as nasal decongestant only, since nasal examination using nasopharyngoscope are very expensive. So if there is very small posterior nasal polyp could not be observed. When there was symptoms of sinusitis, however, sinus X- photo was performed.

APPLICATION

The result of this study provide information about the effectiveness of 8 mg Chlorpheniramine as a once daily regimen in terms of relieving symptoms of perennial allergic rhinitis. Comparison with 10 mg Cetirizine in this study gives an information whether 8 mg Chlorpheniramine at bedtime has no difference success result compared to 10 mg Cetirizine in terms of relieving symptoms and adverse effects or not. The severity of symptoms rely on the patients information (self record) of out patients, so application of this study in children would be limited.

The cost-effectiveness analysis of this study provide information which one is more cost effective, once a day of 8 mg Chlorpheniramine or 10 mg Cetirizine in the treatment of perennial allergic rhinitis patients.