CHAPTER 4

RESULTS

PATIENTS ACCOUNTING

Up to February 18, 1999 , there were a total of 233 perennial rhinitis patients who fulfilled the eligible criteria and were willing to join the study. Although the number of the patients were less than the sample size that was planned before, the result was analyzed only for learning, not suitable for the interim analysis that should be planned before.

Among the 233 patients who completed the first week run-in period, 117 patients received budesonide 400 micrograms daily and 116 patients received budesonide 200 micrograms daily. Data from 20 patients were incomplete because the patients did not come for the follow-up after receiving the intervention drug and the researchers could not contact them either by telephone or by mail. These patients were counted as the dropouts. Another one patient came for the follow up only at the first week with the successful result, however, she did not come after the second visit. So the overall dropouts rate was 9% (21/233). The remaining 212 patients followed the protocol till the end of the study, being 105 patients in the 200 micrograms daily group and 107 patients in the 400 micrograms daily group.

DEMOGRAPHIC DATA

There were 110 males and 123 females involved in the study, ages ranged from 16-68 years old (mean = 30.2, S.D.=10.1). Before and after excluding the dropouts , the baseline characteristics of both groups were similar in terms of age, sex ,duration of chronic nasal symptoms, types of occupation and the mean daily individual nasal symptom score.(tables 1,2,3) The dropout rates were 9.5%(11/116) and 8.5%(10/117) in the 200 micrograms daily group and 400 micrograms daily group respectively. After excluded the dropouts, there were 212 who completed the trial. Among these patients, 210 had the mean baseline individual nasal symptom score less than 2 while only two patients had the mean baseline individual nasal symptom score at least 2. The compliances of using nasal spray of both groups were similar, (mean = 95%) for both groups. As reported by the patients, there were no contamination and co-intervention of both groups. The numbers of patients with upper respiratory tract infection attack at one or more occasion after using budesonide nasal spray in both groups were similar, 9 patients in 200 micrograms group and 6 patients in 400 micrograms group.

Table 1. Demographic data for the total studied patients

	DOSE 200 mcg/day	DOSE 400 mcg/day
TOTAL NUMBER of patients	116	117
SEX: male: female	55:61	55:62
AGE mean ± S.D.	29.8 ±10.1	30.6 ±10.0
median	29.0	29.0
range	16-68	16-57
Duration of nasal symptom:		
mean ± S.D.	6.6 ± 5.2	6.4 ± 6.1
median	5.0	5.0
range	1-20	1-30

Occupations		
Government officers	36	39
Housewife	8	8
Merchants	12	10
Students	40	39
Industrial workers	0	1
White collars	4	8
Farmers	9	6
Others	6	4

Table 2. Demographic data for the studied patients , excluding the dropouts

	DOSE 200 mcg/day	DOSE 400 mcg/day
TOTAL NUMBER of patients	105	107
SEX: male: female	46:59	52:55
AGE: mean ± S.D.	29.4 ± 9.9	30.3 ±10.0
median	29.0	28.0
range	16-68	16-57
Duration of nasal symptom:		
mean ± S.D.	6.5 ± 5.0	6.6 ± 6.3
median	5.0	5.0
range	1-20	1-30
COMBINED INDIVIDUAL NASAL SCORE		
DURING RUN-IN PERIOD	3.6 ± 1.5	3.3 ± 1.3
congestion	1.3 ± 0.7	1.2 ± 0.6
nasal discharge	1.4 ± 0.6	1.3 ± 0.5
sneezing	1.0 ±0.6	0.9 ±0.5
% of using nasal spray (compliance)		
means ± S.D.	95 ± 7.6	95 ± 8.3
median	100	100
range	67-100	57-100

Table 3. Demographic data of the dropouts

	DOSE 200 mcg/day n=11	DOSE 400 mcg/day n=10
SEX: male:female	9:2	3:7
AGE: mean ± S.D.	34 ± 12	33.2 ± 10.7
median	35.0	35.0
range	18-56	19-48
DURATIONS OF NASAL SYMPTOMS		
mean+/-S.D.	7.7 ± 5.9	4.6 ± 3.4
median	6.0	4.0
range	2-20	1-10
COMBINED INDIVIDUAL NASAL SCORE		
DURING RUN-IN PERIOD	3.6 ± 1.3	3.3 ± 2.0
congestion	1.2 ± 0.6	0.9 ± 0.7
nasal discharge	1.4 ± 0.5	1.4 ± 0.9
sneezing	1.0 ± 0.6	1.1 ± 0.9

EFFECTIVENESS OF TREATMENT

The analysis of this study followed a principle of intention-to-treat. The analysis depended on the outcome measurement.

1. Primary outcome measurement: total nasal symptom scale

There were two ways of using the total nasal symptom scale

1.1 Use as original five ordered categorical data and binary data at each end point.

When analyzed as the five ordered categorical data (table 4), the results revealed statistically and clinically significant difference between the two dosages of budesonide at every endpoint. These findings were confirmed when collapsing the five ordered categorical data into binary data , for clinical understanding, it showed using budesonide 400 mcg daily were more clinically and statistically significant effective than using budesonide 200 mcg daily at the end of the 4th week(3 week after spraying the nose) with the 95% confidence interval of the percent success difference between1.3% and 24% (table 5). The difference of the percent success between the dosages at the end of the trial were more effective for the 400 mcg daily groups when assuming the results of the dropouts of both groups into the worst and best cases except when assuming all the dropouts in the 200 mcg daily were success and all the dropouts in the 400 mcg daily were all failure which would be quite impossible because the higher dose will not be less effective than the lower dosage. (table 6)

Table 4. Patients' assessment of treatment effectiveness by total nasal symptoms assessment, expressed in percentage.

Patients' assessment	2nd week		3rd week		4th week	
	Dose1 (n=105)	Dose2 (n=108)	Dose1 (n=105)	Dose2 (n=107)	Dose1 (n=105)	Dose2 (n=107)
1.Worse	1.0	0.9	1.0	0.9	1.0	0
2.The same	19.0	14.8	11.4	7.5	9.5	8.4
3.Slightly controlled	37.1	27.8	21.9	16.8	20.0	9.3
4.Substantially controlled	28.6	29.6	41.9	34.6	43.8	41.1
5.Totally controlled	14.3	26.9	23.8	40.2	25.7	41.1
Chi-square for trend	4.66		4.7		5.8	
p-values	0.03		0.03		0.02	

Dose1= budesonide 200mcg/day, Dose2= budesonide 400mcg/day

Table 5. Percents of patients by collapsing the total assessment into two binary outcome at each endpoint.

	2nd week		3rd week		4th week	
	Dose1 (n=105)	Dose2 (n=108)	Dose1 (n=105)	Dose2 (n=107)	Dose1 (n=105)	Dose2 (n=107)
Failure	57.1	44.0	34.3	25.2	30.5	17.7
Success	42.9	56.0	65.7	74.8	69.5	82.2
95%C.I.ofsuccess difference(dose2-dose1)	(-0.2) – 26.4		(-0.3)-21		1.3-24	
P-value	0.06		0.14		0.03	

Dose1 = budesonide 200 mcg/day Dose2=budesonide 400 mcg/day

Table 6. The difference of the results between two dosages when vary the results of the dropouts by collapsing the total symptom assessment into binary data at the end of 4th week.

		Dose 200 mcg/day	
		All dropouts were success	All dropouts were failure
Dose 400 mcg/day	All dropouts were success	95% C.I.*=1.4%-22.5% P-value =0.03	95%C.I.*=9%-31.9% P-value =0.0003
	All dropouts were failure	95% C.I.*=(-8.5%)-14% P-value =0.06	95% C.I.* =0.7%-24.2% P-value = 0.04

* = 95% confidence interval of the success difference in percents (dose 400 –dose200)

1.2 Analyzed the total nasal symptom score data as the longitudinal data (repeated measures) by using generalized estimating equations (GEE) statistics

The measurements of total nasal symptoms were conducted by the patients assessed themselves repeatedly once a day. The nasal symptoms on everyday were not independent but were the dependent variables. Therefore it was necessary to take into account correlation or clustering between everyday nasal symptoms "within" the same patient. This was accomplished using the Generalized Estimating Equation (GEE) approach of Liang and Zeger.[37]

Because of the limitation of the software for analyzing the result of the two treatments for repeated ordinal outcome measurement, this study used the STATA® Statistical Software version 5.0 using GEE by collapsing the repeated ordinal data of every day assessment into binary outcome. If the total symptoms were 0-2, it would be failure and if it was 3-4 it will be success. It revealed the success rate of using budesonide 400 mcg daily was 1.19 times that of using budesonide 200 mcg daily which was statistically significant (table 7) with the 95% CI of the difference of success rate between 1.01-1.4 times

Table 7 Statistical analysis using GEE by collapsing the patients' total nasal symptom scales into the binary data

total symptom	e^coef	Std. Err.	z	P>|z|	[95% Conf.	Interval]
dose	1.18738	.0982363	2.076	0.038	1.00964	1.396409

2.Individual nasal symptom score

This thesis used the individual nasal symptom score as the continuous score which is accepted among the experts in order only for the exploratory purpose. The statistics to be used is the unpaired t-test. The statistical significant differences between the two dosages were found only for the nasal dischage symptom at each end point but there were no statistical significant differences for nasal congestion and sneezing. When

combined all nasal symptoms together, there were statistical significant differences at the end of the 3rd and 4th week. (table 8)

Table 8. Statistical analysis using individual nasal symptoms score as continuous data

	200mcg/day		400mcg/day		Difference of significance
	Mean	S.D.	Mean	S.D.	P-values
1st week (run-in)					
1.Congestion	1.27	0.67	1.17	0.64	0.28
2.Nasal discharge	1.35	0.62	1.28	0.53	0.38
3.Sneezing	0.95	0.64	0.89	0.52	0.40
4.Combined (1+2+3)	3.57	1.46	3.34	1.28	0.21
2nd week					
1.Congestion	0.73	0.64	0.64	0.65	0.30
2.Nasal discharge	0.79	0.61	0.63	0.55	0.048*
3.Sneezing	0.39	0.39	0.32	0.35	0.16
4.Combined	2.02	1.40	1.68	1.33	0.74
3rd week					
1.Congestion	0.63	0.61	0.54	0.60	0.29
2.Nasal discharge	0.61	0.54	0.45	0.43	0.015*
3.Sneezing	0.49	0.46	0.41	0.42	0.17
4.Combined	1.73	1.25	1.40	1.14	0.04*
4th week					
1.Congestion	0.58	0.60	0.49	0.56	0.24
2.Nasal discharge	0.61	0.54	0.49	0.43	0.015*
3.Sneezing	0.35	0.35	0.29	0.32	0.15
4.Combined	1.55	1.18	1.23	1.05	0.035*

EVALUATION OF THE ADVERSE EFFECTS

The adverse reactions were found in 40%(81/212). Although the incidence rate was rather high, they are the very minor effects and nobody had to stop the drugs. Comparing the adverse reactions between the two dosages, the events occurred similarly and there were no clinically and statistically significant differences (Table 9).

Table 9. Numbers of patients reporting adverse events on one or more occasions .

	200mcg/day (n=105)	400 mcg/day (n=107)	95%C.I. proportional difference (dose 400-dose200)	P-values
Number of pts	45%(47)	35%(37)	(-0.21)-0.05	0.24
Adverse events:				
1.Nasal irritation	19%(20)	18%(19)	(-0.11)-0.09	0.8
2.Dry nose	21%(22)	19%20	(-0.13)-0.09	0.8.
3.Dry throat	20%(21)	22%(24)	(-0.09)-0.13	0.7
4.Itching nose	17%(18)	14%(15)	(-0.13)-0.07	0.6
5.Sneezing	12%(13)	17%(18)	(-0.04)-0.14	0.3
6.Epistaxis	0	0		

ECONOMIC EVALUATION

Because budesonide nasal spray has to be imported and it is quite expensive, the cost analysis in this thesis was performed on the viewpoint of health provider . The direct non-medical costs and indirect costs such as transportation, parental work loss was not be included because these costs were the same in both groups of using budesonide.

Costs were determined for the fiscal year 1998 and expressed in Baht for each intervention encountered in each alternative as.

1. Unit costs

The unit cost for the ENT outpatient department had been studied by Vatanasapt et al[38] and found to be 67 baht/case.

2. Costs of budesonide

The price for one bottle of budesonide aqueous nasal spray either 50 mcg/puff or 100 mcg/puff was 240 baht. However, because the patients in this study could use the 50 mcg/puff bottle two times longer than budesonide 100 mcg/puff bottle. The price for calculating the cost-effectiveness should be half of the full price.

3. Costs for treating adverse reactions

Owing to the very minor adverse reactions, nobody stopped the medications or needed other medications to treat these events. So the cost of treating the adverse reactions was not taken into account.

The success rate at the end of the third week after treatment were 70 % and 82% for the dosage of 200 micrograms and 400 micrograms respectively(table 5).

Analysis

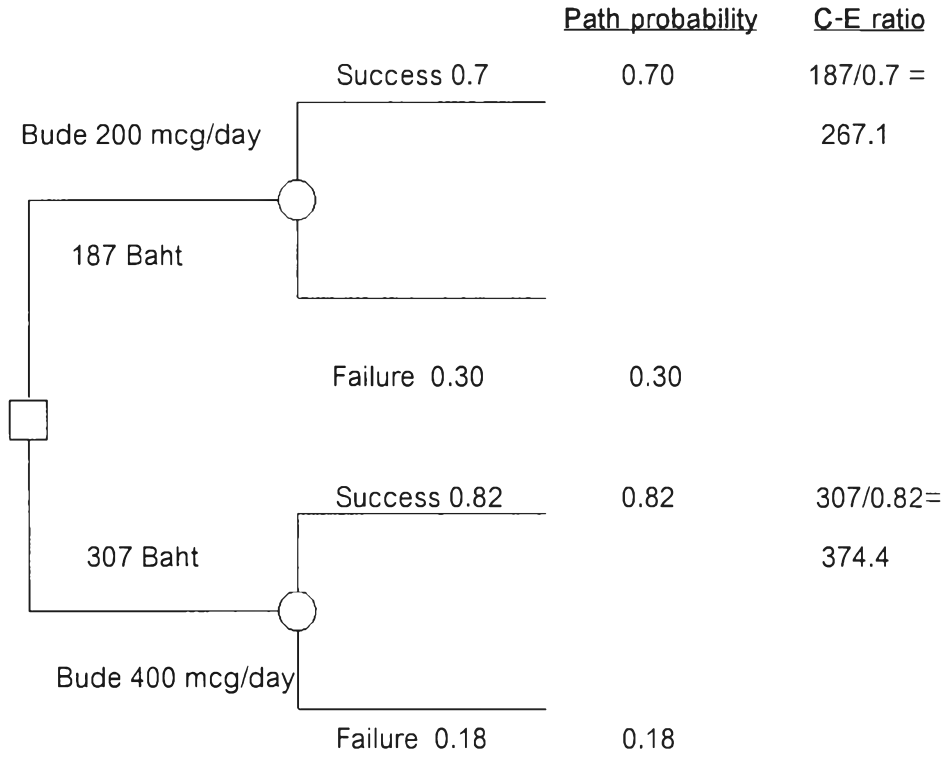
The expected costs for each patient in either group were 1 unit cost + cost of budesonide. The expected total cost for each patient in the 200 mcg/day dosage was 240/2+67=187 Baht and for the 400 mcg/day dosage was 240+67=307 baht.

Cost-effectiveness (C.E) ratio (figure 2)

The cost-effectiveness ratio for each alternative was calculated by using the expected cost divided by the probability of success . It showed that using budesonide

200 micrograms daily was more cost-effective than 400 micrograms daily.

Figure 2. The expected cost, path probability of each alternative and cost-effectiveness ratio



Marginal cost-effectiveness

Marginal cost-effectiveness was calculated by using the following formula

Margical cost-effectiveness = (cost1-cost2)/ (effectiveness1- effectiveness2)

= (307-187)/ (0.82-0.7)

= 119.88 Baht/ one additional success patient

Sensitivity analysis

C-E ratio was analyzed by varying the success rate of budesonide 200 and 400 micrograms group according to the 95% C.I. of success rate. At the end of the trial, the

95% success rate of budesonide 200 micrograms group and 400 groups were 0.61-0.78 and 0.75-0.9 respectively. The sensitivity analysis was shown in figure 3 showing that using budesonide 200 micrograms daily was still more cost-effective

Figure 3. Sensitivity analysis by varying the effectiveness of both dosages of budesonide