

CHAPTER 5

DISCUSSION

Although perennial rhinitis is a chronic non-fatal diseases , the patients with this disorder may be disturbed by the chronic nasal symptoms throughout the year. The prevalence of this disease is quite high around the world. Although the allergen and irritant avoidances are the ideal way for prevention, it is very difficult to avoid these factors because most of the allergens and irritants are air-borne. One of the most practical way for the management of perennial rhinitis is pharmacotherapy in order to control the nasal symptoms .

Budesonide nasal spray is one of the most favorite drug for perennial rhinitis. Many studies showed that it was very effective comparing with other medications. Nowadays the recommended dose for adults with perennial rhinitis is 400 micrograms per day. The rationale for using budesonide 400 micrograms daily in adults derived from the studies showing that budesonide 400 mcg daily was more efficacious than 200 micrograms daily and has the same efficacy as 800 micrograms daily.^{3,4,11,14,30,31}

The effectiveness of budesonide from this study could be summarized as

1. Total nasal symptoms assessment
 - Ordered five categorical data : clinical & statistically significant difference
 - Collapse as binary data: clinical & statistical significant difference only at the end of 3rd week after using budesonide nasal spray (95% C.I. of success difference = 1.3%-24%)

- Repeated binary data using GEE : clinical & statistical significant difference. The effectiveness of using budesonide 400 micrograms daily were 1.19 times that of using budesonide 200 micrograms daily (95% C.I.=1.01-1.4, P-value = 0.038).

2. Individual nasal symptoms

The statistical significant differences between the two dosages were found only for the nasal discharge symptom at any 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.

This study showed that using budesonide aqueous nasal spray 400 micrograms daily was more effective than using 200 micrograms daily. There were few studies comparing budesonide 200 micrograms daily with 400 micrograms daily for perennial rhinitis and other similar nasal disorders (table10). All of the studies claimed that budesonide 400 micrograms were more effective than 200 micrograms daily. However the primary outcome measurements used in the above articles were individual nasal symptom score which in fact the individual nasal symptom score is the ordinal scale but all of the published articles about clinical trial of rhinitis used it as the continuous data which is very difficult to understand for the clinicians. Nevertheless this study also analysed the individual nasal symptom score in order to compare with the result of the previous studies. By treating the individual nasal symptom score as continuous data, this study revealed that budesonide 400 micrograms daily can control nasal discharge more effective than 200 micrograms daily at every end point. But there were no difference in controlling nasal stuffiness and sneezing. When combined the score of all nasal symptoms together, it showed that 400 micrograms can control nasal symptoms more effective only at the 3rd week of using nasal spray. This result was the same as

other studies.^{7,14,30} However, as mentioned above, the magnitude of difference has been meaningful only in statistics, not in clinical aspects.

The outcome measurement that is easier to understand clinically is the total nasal symptom assessment. However this outcome measurement was usually assessed only at one end-point as if it were independent on time. In fact it should be the dependent measurement. There was two studies comparing budesonide 200 micrograms and 400 micrograms daily that also used total nasal symptom assessment. They showed that there were no statistically significant differences between the two dosages.^{15,30} This study used the statistic of "Chi-square test for trend" for the five ordered categorical data because this statistic is used to compare frequencies or proportions among groups which have an ordering and it is reasonable to make use of the ordering to increase the power of the statistical analysis. Chi-square test for trend is a powerful method of analysis because it yields a test statistic from a Chi-squared distribution with one degree of freedom rather than $k - 1$ degrees of freedom for the usual Chi-square test. It revealed that using budesonide 400 micrograms daily was clinical and statistical significant more effective than using 200 micrograms daily at any end point.

When collapsed ordered five outcome categories into two binary outcome as success and failure, it showed that using budesonide 400 micrograms daily was still clinical and statistical significant more effective than using 200 micrograms daily at the end of the trial. However the reason for collapsing an ordinal outcome variable in this study was the easily understanding for the clinician but the primary results were still rely on the ordered five categorical data because the power of the statistical analysis is less if collapsing an ordered outcome categories.

This study differed from other previous studies because the patients had to assess the total nasal symptoms everyday comparing daily total nasal symptoms with their baseline symptoms. This measurement was the repeated ordinal data, so generalized

estimating equations (GEE) statistic was used. The repeated measures design is generally more efficient for determining a treatment effect when compared with completely randomized designs,³⁹ with efficiency increasing with increases in the (positive) correlation between the repeated measures. However because of the limitation of the statistical software, this study collapsed the repeated five ordered outcome categories into two binary outcome and used STATA[®] Statistical Software version 5.0 for computations of GEE. The overall effect of budesonide when analyzed by adjusted for clustering on patient only (crude effect) also showed that budesonide 400 micrograms were statistical and clinical significant more effective than 200 micrograms.

The adverse reactions in this study occurred quite high comparing with other studies.^{9,14,30} However it was the only minor effects and did not disturb the patients. Every patients who reported the occurrence of adverse reaction could continue to use budesonide and did not need any additional medications to treat these effects. The serious adverse reactions such as epistaxis, nasal septal perforation and fungal infection were not founded.

For economic analysis, although it showed that using budesonide 200 micrograms daily was more cost-effective, as shown by cost-effectiveness ratio and sensitivity analysis, than budesonide 400 micrograms daily, the clinicians may not change their practice because using budesonide 400 micrograms daily was more effective than 200 micrograms daily.

Table 10. Summarize the studies comparing budesonide 400 micrograms daily and 200 micrograms daily.

| | Study design | Outcome measures | Types of scale used | Time of assessment | Result |
|-------------------------------|-------------------------|------------------|--|--------------------|--|
| Balle et al. ⁷ | Randomized double-blind | INS | Use ordinal as continuous | Each end point | 400mcg/d > 200mcg/d |
| Pedersen et al. ¹⁵ | RCT | 1.INS. 2.TS | 1.INS as continuous 2.TS as categorical | Each end point | 400 > 200 mcg/day for ins but for TS no statistically significant. |
| Irandar et al. ³⁰ | Single blind | 1.INS 2.TS | 1.INS as continuous 2.TS as categorical | Each end point | Same as above |

INS = individual nasal symptom score, TS = total nasal symptom score