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A Clinical Comparison of Budesonide Nasal Aerosol, Terfenadine and a Combined Therapy of Budesonide and Oxymetazoline in Adult Patients with Perennial Rhinitis

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SUMMARY **The efficacy of budesonide, terfenadine and a combination of budesonide and oxymetazoline in the treatment of perennial rhinitis was evaluated by a double blind, parallel group study. Adult patients with perennial rhinitis were randomized into three groups. Group 1 patients received budesonide nasal aerosol 400 μg/day for 21 days and oxymetazoline nasal drops for the first three days. Group 2 and 3 patients received budesonide 400 μg/day and terfenadne tablet 60 mg twice/day respectively. Nasal symptoms were assessed by the patients before and daily during the treatment period using a simple scoring system. One hundred and forty-two patients were recruited and 130 completed the study. Budesonide, but not terfenadine, significantly reduced all nasal symptoms from baseline ($p < 0.05$). Terfenadine could significantly relieve the nasal blockage ($p < 0.05$) more than other nasal symptoms. Budesonide with or without oxymetazoline nasal drops provided a better control of nasal symptoms than terfenadine ($p < 0.05$). Budesonide with oxymetazoline for the first three days showed a faster relief of nasal blockage than budesonide alone ($p < 0.05$). Mild and transient adverse effects were encountered in all three groups. It is concluded that nasal symptoms of perennial rhinitis are more adequately controlled by budesonide than by terfenadine.**

Topical intranasal corticosteroid and antihistamine have become established drugs in the treatment of perennial rhinitis. Budesonide is a non-halogenated steroid with a high local anti-inflammatory effect and is more efficiently inactivated in the liver than the halogenated steroids.[1,2] Budesonide has been shown to have a high ratio of topical to systemic activity compared with a number of reference corticosteroids such as be clomethasone dipropionate, flunisolide and triamcinolone.[2-5] There have been a few studies comparing the efficacy of budesonide and various topical intranasal corticosteroid preparations in the treatment of rhinitis. The results of some of these studies, revealed that budesonide were more effective than beclomethasone dipropionate.[6-9] Intranasal budesonide has been progressively used and results of long term open trials have shown that it is effective and safe in the treatment of perennial rhinitis.[10-12]

Antihistamine is a widely used drug in the treatment of perennial rhinitis. However the older generation of antihistamine usually has sedative effects. Terfenadine is a new generation of potent H1-receptor antagonist without any sedative effects.[13,14] Although budesonide and terfenadine have been reported to be more efficient in the treatment of perennial rhinitis than their older counterparts, a direct comparison between their efficacy in Chinese patients have not been studied. There have been a few studies directly comparing topical intranasal corticosteroid with the H1-antagonist in the treatment of seasonal allergic rhinitis. Most of these studies showed that topical intranasal corticosteroid provide a better control of nasal symptoms than terfenadine.[15-17] A few studies show that astemizole and beclomethasone dipropionate are as good as each other in treatment of allergic rhinitis.[18,19]

It seemed, therefore, relevant to carry out a double-blind study to

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compare the efficacy of budesonide and terfenadine in the treatment of perennial rhinitis in adults. In this disease, the nasal mucosa is usually congested which prevents an even distribution of the topical steroid applied by nasal aerosol. Vasoconstrictor nasal drops shrink the nasal mucosa so that the topical corticosteroid which is administered shortly afterward can be more evenly distributed. Therefore the use of such nasal drops for the initial few days may have an enhancing effect on the topical corticosteroid treatment. Thus another aim of this study was to investigate the effect of additional vasoconstrictor nasal drops (oxymetazoline) for the first three days on the efficacy of budesonide treatment.

MATERIALS AND METHODS

Design

The study was conducted in the Otorhinolaryngological Clinic of University of Hong Kong and Chinese University of Hong Kong. The study was of double blind, double dummy and randomized parallel groups design. Patients with perennial rhinitis were randomized at entry into three groups. The study design is shown diagramatically in Fig. 1. Patients of Group 1 received budesonide nasal aerosol 200μg twice daily and terfenadine placebo for 21 days. During the first three days,they also received three drops of oxymetazoline nasal drop pipette (0.5 mg/ml) 15 minutes before the administration of the budesonide nasal aerosol. Patients of Group 2 received budesonide nasal aerosol, terfenadine placebo and oxymetazoline placebo. Patients of Group 3 received terfenadine tablet 60 mg twice daily, budesonide placebo and oxymetazoline placebo. The study was designed in such a way that the patients would receive active treatment of one sort or the other. No patient would receive placebo alone.

Inclusion Criteria

The inclusion criteria were as follows: the patient's age should be between 15 and 70; the patients should have symptoms of perennial rhinitis for at least two years preceding the study; the patients should have blocked nose or two of the following symptoms, runny nose, itchy nose or sneezing bouts; the patients should have given verbal or written consent.

Exclusion Criteria

Patients who received other steroid treatment at any time during the study or during the preceding four weeks were excluded. Patients who signs of bacterial, viral or fungal infection at trial entry were excluded. Patients with septal deviation or nasal polyps were excluded. Nursing or pregnant patient would not be included.

Assessment

Assessment were made three times in the clinic and continuously during this study. At entry patients quantified their nasal and eye symptoms during the previous 24 hours according to the following scoring system:

0 = no symptoms
1 = mild symptoms (present but not troublesome)
2 = moderate symptoms (frequently troublesome but not sufficient to interfere with daily activity or sleep)
3 = Severe symptoms (sufficiently troublesome to interfere with daily activity or sleep)

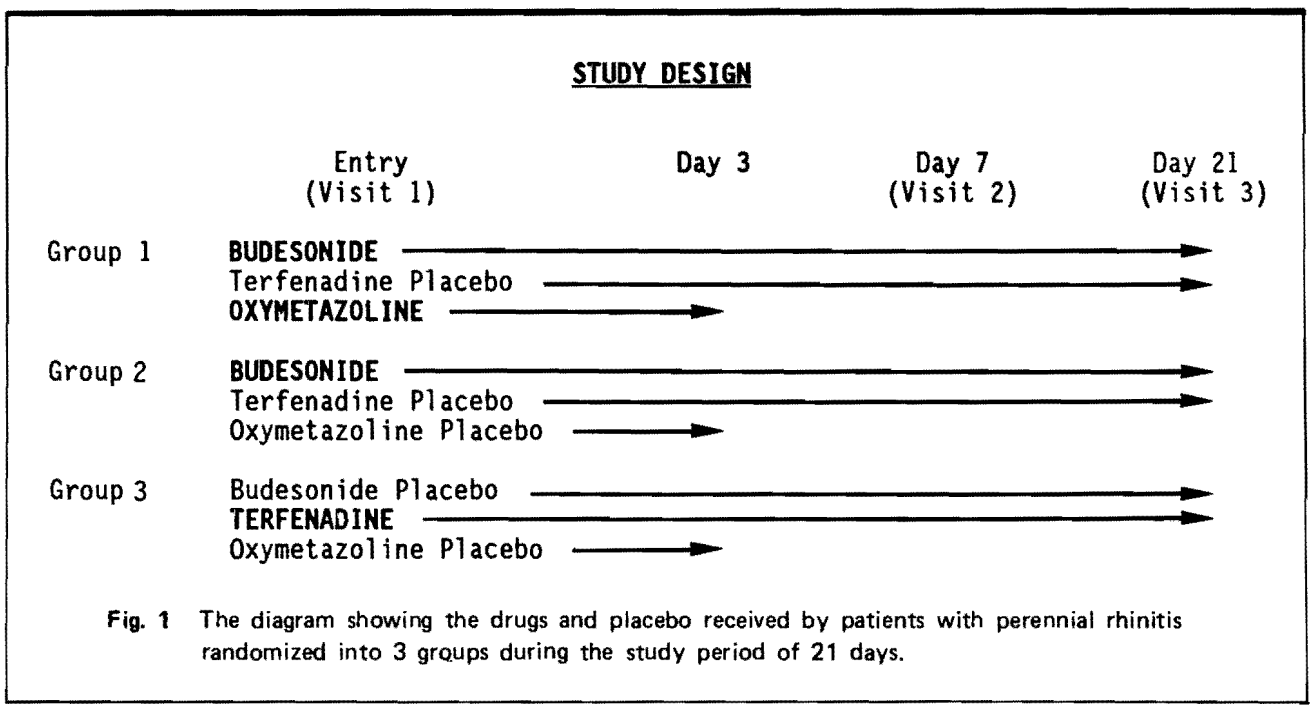

Fig. 1 The diagram showing the drugs and placebo received by patients with perennial rhinitis randomized into 3 groups during the study period of 21 days.

The symptoms recorded were blocked nose, runny nose, itchy nose, sneezing bouts, sore eyes and runny eyes. Each night before going to bed, the patients assessed their symptoms during the previous 24 hours and recorded the symptom score in a diary card. Any other symptoms or adverse effects experienced by the patients were noted in the diary cards. The patients returned to the clinic after one and three weeks when the diary cards were checked and grading of symptoms were made. Adverse effects experienced by the patients were enquired about in the clinic with a non-leading question: "How have you felt since the start of the treatment?" At the final visit, the patients made a global assessment of previous three weeks of treatment using a four graded scale: ineffective, slightly, moderately and extremely effective. Wilcoxon's rank sum tests were used for the analysis of data.

RESULTS

Between June 1986 and May 1988, 142 patients were recruited. Sixty-five were male, 77 were female. All of them were ethnic Chinese except two who were ethnic Indian. The mean age was 26.7 year, ranging from 15 to 68. 47, 48 and 47 patients were randomized into Group 1, 2 and 3 respectively. The three groups of patients were comparable in their age, sex and symptom score. There was no statistically significant difference in all symptom scores among the three groups when entered into the study. It should be noted that the mean symptom score in the present study were of low grading for all symptoms (Fig. 2,3,4,5). One hundred and thirty patients completed the study. By comparing symptom score at entry with daily symptom score of each week, it was found that budesonide significantly reduced all the nasal symptoms from the base line ($p < 0.05$) (Fig. 2,3,4,5). Terfenadine could significantly relieve nasal blockage ($p < 0.05$). However the relief of the other nasal syptoms by terfenadine was not statistically

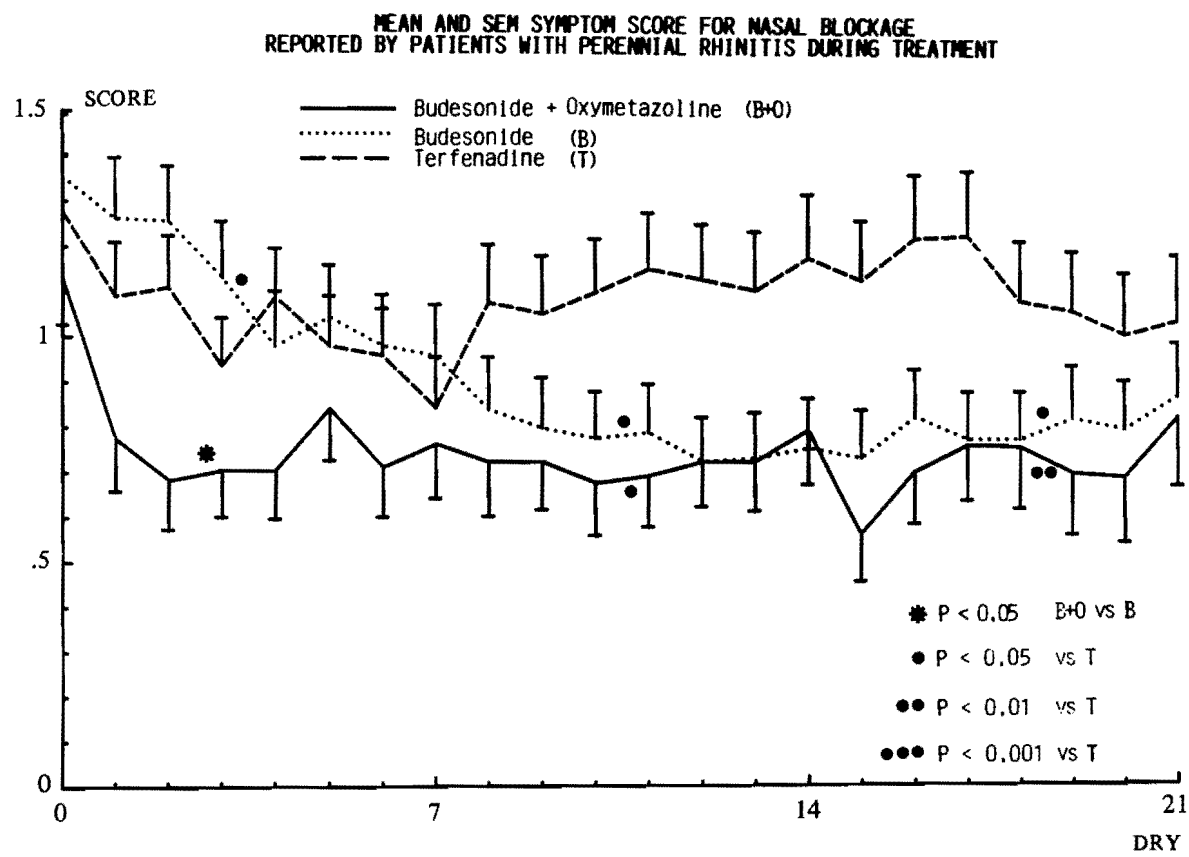

Fig. 2 Mean and SEM of daily symptom score for nasal blockage reported by patients with perennial rhinitis during treatment. (The daily symptom score of each week was compared with those receiving other form of treatment using Wilcoxon's rank sum test).

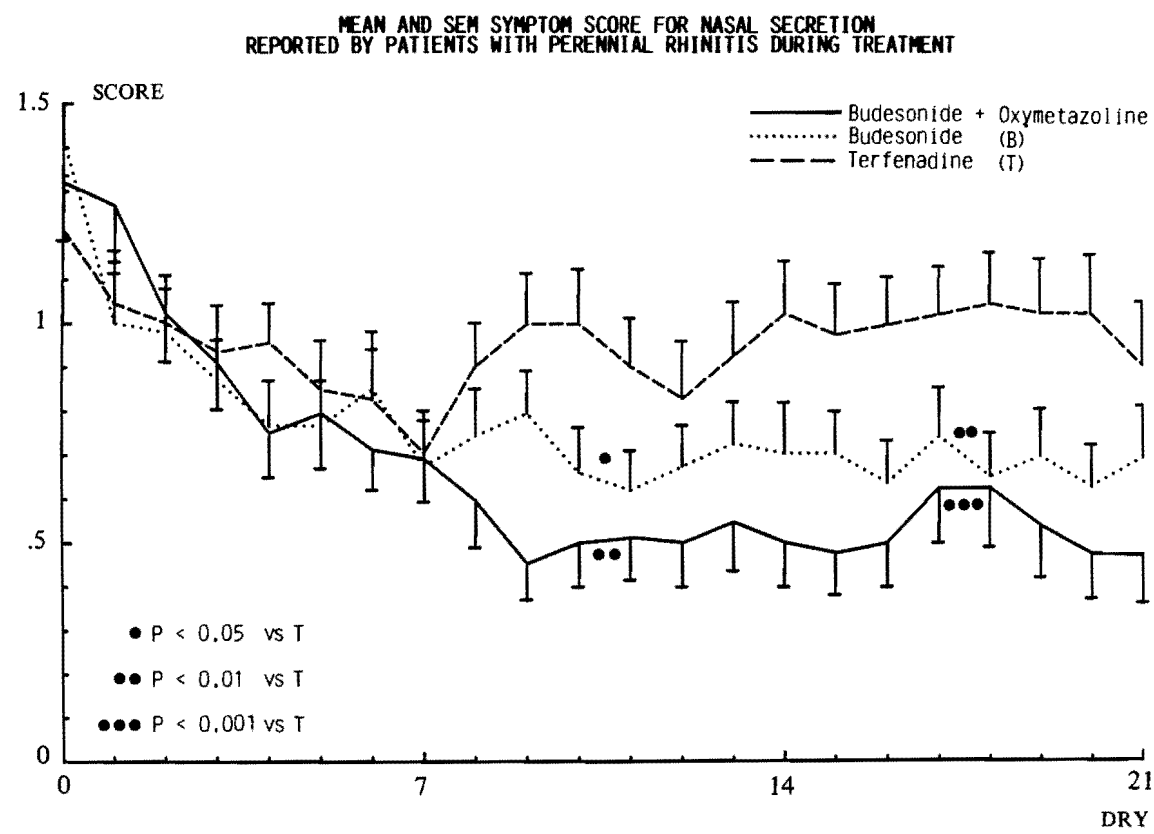

Fig. 3 Mean and SEM of daily symptom score for runny nose reported by patients with perennial rhinitis during treatment. (The daily symptom score of each week was compared with those receiving other form of treatment using Wilcoxon's rank sum rest)

significant. Budesonide, with or without oxymetazoline nasal drops provided a better control of the nasal symptoms than terfenadine. This difference was statistically significant ($p < 0.05$) when the daily symptom score of each week of the group 1 or 2 was compared with group 3.

Budesonide nasal aerosol in combination with oxymetazoline nasal drops for the first three days showed a faster relief of nasal blockage than budesonide alone (Fig. 2). With budesonide alone it took seven days to reach maximal relief of nasal blockage whereas budesonide coupled with oxymetazoline nasal drop relieved the nasal blockage after one day. The difference is statistically significant ($p < 0.05$). Most patients had minor

Table 1. Adverse effects experienced by patients with perennial rhinitis receiving different forms of treatment.

	Budesonide + Oxymetazoline	Budesonide	Terfenadine
Nasal irritation	2	3 (1)	3
Throat irritation	1	0	0
Headach	2 (1)	2	0
Dizziness	0	1	1
Nausea	0	1	1
Dry mouth	0	0	1
G–I distress	1	2	10 (2)
Others	0	1	1
Total	6	10	17

(n) = number of patients withdrawn because of the adverse effect.

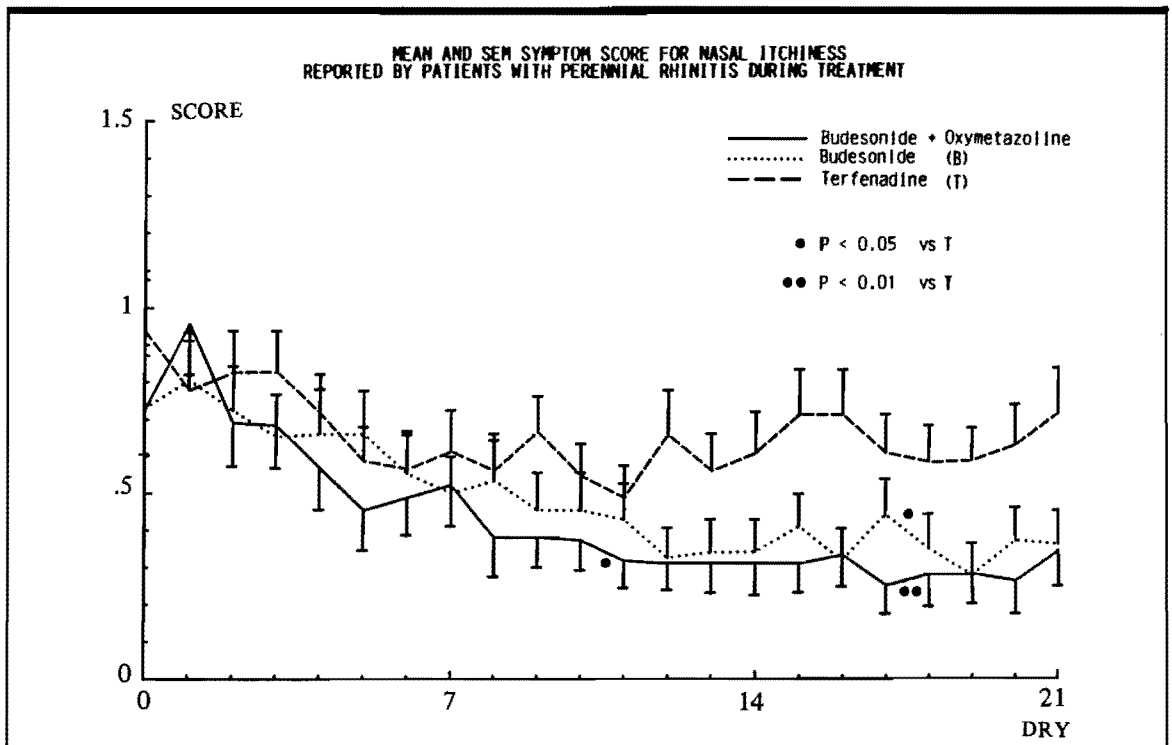

Fig. 4 Mean and SEM of daily symptom score for itchy nose reported by patients with perennial rhinitis during treatment. (The daily symptom score of each week was compared with those receiving other form of treatment using Wilcoxon's rank sum test).

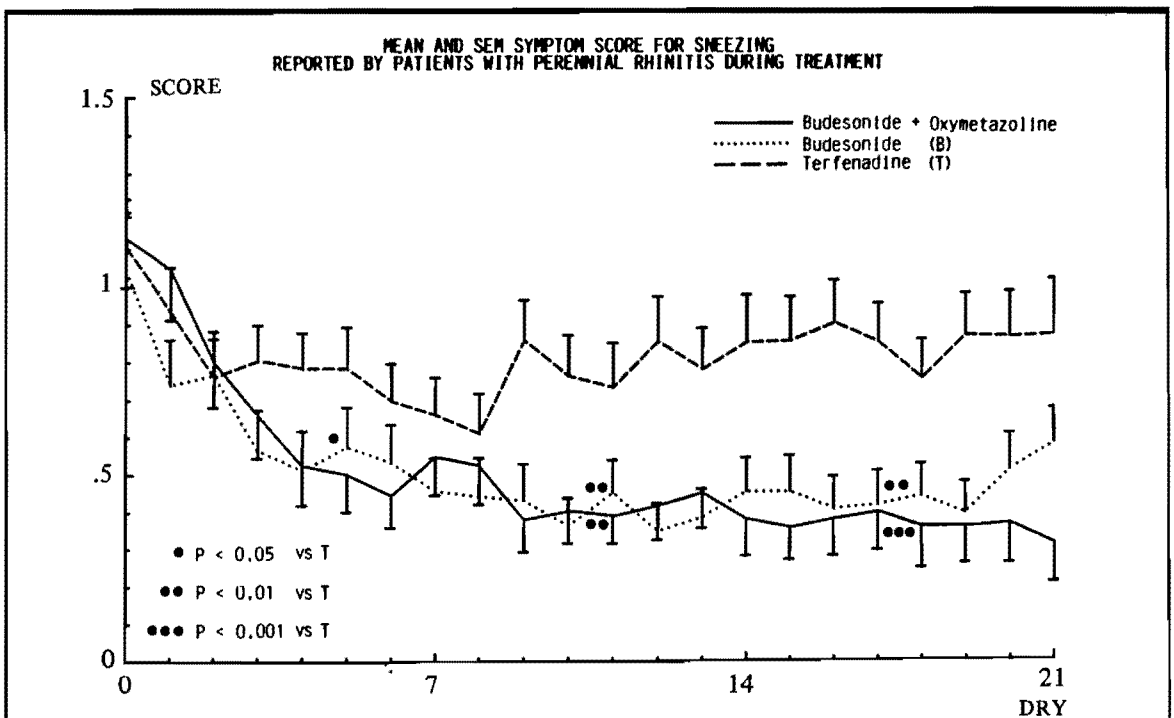

Fig. 5 Mean and SEM of daily symptom score for sneezing bouts reported by patients with perennial rhinitis during treatment. (The daily symptom score of each week was compared with those receiving other form of treatment using Wilcoxon's rank sum test).

eye symptoms when they entered the study. No differences in the treatment efficacy was seen among the three treatment groups regarding the eye symptoms. There was no significant difference in the global assessment of treatment efficacy made by the three groups of patients.

Adverse effects were mild and transient. These included nasal irritation, throat irritation, headache, dizziness, nausea, dry mouth, gastro-intestinal upset and other (Table 1). In most of the patients the side effects were so mild that the patients could continue with the medication. Ten patients who received terfenadine had gastrointestinal complaints. Thus the incidence of adverse effects from gastrointestinal tract in this group was high. None of those who received terfenadine complained of sleepiness. Twelve patients did not complete the study for various reasons. Four of them withdrew because of side effect of the medication. One had severe nasal pain after using budesonide nasal aerosol for seven days. Another one complained of headache after using budesonide aerosol.. Two developed ulcer pain after taking terfenadine tablets for seven days. Eight patients defaulted follow up during the study (i.e. drop-out).

DISCUSSION

The study was designed in such a way that all patients would receive active treatment no matter which group They were randomized into. This design is ethically more acceptable because no patient would receive placebo alone. This design aimed to reduce the drop-out rate because every patient received either budesonide or terfenadine which were known to be effective in treatment of perennial rhinitis. Patients were more willing to return to the clinic when they had received effective treatment. In fact the drop out rate in this study was only 8/142 = 6 percent.

Budesonide nasal aerosol has been used in the treatment of seasonal allergic, perennial allergic and perennial non allergic rhinitis. In patients with seasonal allergic rhinitis budesonide nasal aerosol was more effective than intranasal beclomethasone dipropionate [7] and significantly superior to oral dexchlorpheniramine. [20] In a long term open trial, budesonide nasal aerosol consistently produced a significant reduction of all nasal symptom and a low incidence of mild and transient side effects in patients with perennial rhinitis. [10] There is no study reported comparing the efficacy of budesonide nasal aerosol with terfenadine in the treatment of Chinese patients with perennial rhinitis. The present study shows that budesonide significantly relieves all nasal symptoms of perennial rhinitis during the three weeks treatment period. However terfenadine is only effective in relieving the nasal blockage. It has no effects on sneezing, rhinorrhoea and nasal itch. This finding of our study is different from previous studies conducted mainly in the West, which found that antihistamines had little effect on nasal obstruction. The difference is probably racial in origin. Previous studies have shown that intranasal corticosteroid is more effective than terfenadine in treatment of seasonal allergic rhinitis. [15-17] The present study showed that budesonide is also more effective than terfenadine in the treatment of perennial rhinitis.

Usually it takes a few days to reach maximal symptomatic relief for patients using topical intranasal corticosteroid. [21,22] In the present study the maximal relief of nasal blockage was reached after seven days of use of budesonide alone. However in patients who received oxymetazoline nasal drops for the initial three days together with budesonide the maximal relief of nasal blockage was reached after one day of use. This symptomatic relief was maintained even when the oxymetazoline nasal drop treatment was completed on the fourth day. The mean nasal blockage score of the first week for the patients using budesonide and oxymetazoline is significantly lower than the patients using budesonide alone. The vasoconstrictor nasal drop can shrink the nasal mucosa thus allowing a more even distribution of the budesonide nasal aerosol. Furthermore the patient's compliance with the combination use of vasoconstrictor nasal drops and topical intranasal corticosteroid may be higher than the latter alone because of the rapid symptomatic relief.

The side effects of either form of treatment are mild and transient. Nasal or throat irritation is a common side effect with the use of topical intranasal corticosteroid. Sedation, which is common among the older generation of antihistamine, is not encountered with the use of terfenadine in the present study. However, ten patients receiving terfenadine complained of gastrointestinal distress. The incidence of such adverse effect in our study comprising Chinese patients was higher than which has been reported (6.5 percent) in Western countries. [23]

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