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Originals

Effect of Oral Procaterol in Combination with Inhaled Corticosteroids in Adult Patients with Bronchial Asthma

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SUMMARY

Background : Bronchial asthma is considered to be a chronic airway inflammatory disease, and inhaled corticosteroids play a central role in controlling airway inflammation. In some patients, however, it is difficult to control symptoms despite the use of moderate to high doses of inhaled corticosteroids. Long-acting inhaled β_2-agonists have recently become available and reconsidered as a controller.

Objectives : To examine whether combination of an inhaled corticosteroid and an oral β_2-agonist can improve symptoms in patients with moderate bronchial asthma whose airway obstructive symptoms cannot be relieved sufficiently by inhaled corticosteroids alone.

Methods : Of outpatients in our hospital with moderate bronchial asthma (step 3) given beclomethasone at a daily dose of 800 μg, whose peak expiratory flow rate in the early morning was 70 % or less of the predicted value, 12 patients were enrolled in the study who showed at least 12.5 % improvement in the forced expiratory volume in one second ($FEV_{1.0}$) after inhalation of 20 μg procaterol (Meptin Air from Otsuka Pharma. Co.) for 15 minutes. Procaterol tablets (Meptin tablets, 50 μg from Otsuka Pharma. Co.) were administered in the morning and before bed for 4 weeks, and change in the peak expiratory flow rate, subjective symptoms, respiratory function, and the number of puffs of the β_2-agonist were evaluated.

Results : The peak expiratory flow rate, FEV1.0, forced vital capacity (% FVC), and airway hyperresponsiveness improved after coadministration of oral procaterol and beclomethasone.

Conclusions : The oral β_2-agonist in combination with an inhaled corticosteroid might improve asthma symptoms better than inhaled corticosteroids alone.

Key Words : oral β_2-agonist, procaterol, bronchial asthma, inhaled corticosteroids, combination therapy

INTRODUCTION

Bronchial asthma is considered to be a chronic allergic inflammatory disease characterized by airway hyperresponsiveness and infiltration of airway inflammatory cells including eosinophils, lymphocytes, and mast cells[1]. Guidelines for the treatment of asthma developed in Japan, Europe, and the United States place importance on the control of airway inflammation, and inhaled corticosteroids play a central role. However, some patients have inadequate control of symptoms despite the use of anti-inflammatory agents, such as moderate to even high doses of inhaled corticosteroids and antileukotriene agents. Thus, these guidelines emphasize not only anti-inflammatory agents but also dilation of the obstructed airways using bronchodila-

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tors[1]. Among the bronchodilators, β_2-agonists are often used as inhalants because of the quick onset of action, promotion of clearance of airway secretions by ciliary movement, enhancement of airway clearance, and ease of use[2]. However, β_2-agonists have only modest anti-inflammatory effects[2]. Moreover, disadvantages of preexisting short-acting inhaled β_2-agonists have been highlighted, including the lack of long-term benefits[3], airway hyperresponsiveness enhanced[4] and symptoms destabilized and the risk of asthma death increased by regular use of the inhalants alone[2]. Therefore, appropriate use of β_2-agonists has been pressed, and a series of new long-acting inhaled β_2-agonists[5,6] and β_2-agonist patch formulations[7] were developed. They have a prolonged bronchodilating effect and thus are highly effective in relieving asthma symptoms at night and in the early morning, preventing morning dip, and improving quality of life (QOL). Long-acting inhaled β_2-agonists in combination with inhaled corticosteroids were shown to be effective in improving symptoms[8~11], and more effective than leukotriene receptor antagonists[12,13]. Thus, the guidelines came to recommend these long-acting β_2-agonists as a controller. Oral β_2-agonists such as procaterol, tulobuterol, and clenbuterol have high selectivity for β_2-receptors and a long duration of action. Unlike inhaled agents, long-term regular use of oral agents has been reported to rarely cause serious adverse reactions, and bronchodilating effect is less likely to wane[2]. These agents do not require special inhalation techniques and offer ease of use and appear to be useful as a controller. However, there are few studies which examined the effect of a combination of an oral β_2-agonist and an inhaled corticosteroid except for bambuterol. Thus, we examined whether a combination of an inhaled corticosteroid and an oral β_2-agonist is effective in improving symptoms in patients with moderate bronchial asthma whose airway obstruction are not well improved by inhaled corticosteroids alone.

METHODS

Among outpatients with moderate (step 3) bronchial asthma given beclomethasone at a daily dose of 800 μg for at least 2 weeks and had a morning peak expiratory flow rate of 70 % or less of the predicted value, patients who showed at least 12.5 % improvement of $FEV_{1.0}$ 15 minutes after inhalation of 20 μg of procaterol (Meptin Air from Otsuka Pharma. Co.) were enrolled in this study. Patients who regularly used oral or inhaled β_2-agonists were excluded. Patients who used systemic corticosteroids during a 2-week run-in period were also excluded. Table 1 shows patients baseline characteristics. Procaterol tablets (Meptin tablets, 50 μg from Otsuka Pharma. Co.) were orally administered in the morning and at bedtime for 4 weeks. The peak expiratory flow rate and respiratory functions (FVC, $FEV_{1.0}$, and $FEV_{1.0}$ %) in the early morning and at bedtime and change in airway hyperresponsiveness were measured 1 week before treatment and at 4 weeks. Peak expiratory flow rates were measured using a Mini-Wright, and the highest of three readings was recorded. Respiratory functions were evaluated with an AutoSpiro (Minato). For assessment of airway hyperresponsiveness, acetylcholine threshold values were used as described in the standard methods established by the Japanese Society of Allergology[1]. Briefly, a DeVilbiss 646 nebulizer driven by compressed air at 5 L/min was used, and patients were instructed to inhale diluted acetylcholine solutions at concentrations of 313 to 20,000 μg/mL stepwise for 5 minutes each. The $FEV_{1.0}$ was measured immediately after inhalation, and the concentration of acetylcholine required to reduce the value by at least 20 % from baseline served as the threshold of acetylcholine. Student's t-test was used for statistical analysis. P values of less than 0.05 were considered a statistical significance.

Table 1 Patient Baseline Characteristics

Sex :	9 males, 3 femal
Age :	58.8 ± 3.4 years
Duration of morbidity :	10.4 ± 2.4 years
Improvement of $FEV_{1.0}$	
after inhalation of procaterol :	26.6 ± 4.2 %
Actual peak flow/predicted peak flow :	66.7 ± 4.8 %

RESULTS

1. Change in the morning peak expiratory flow rate after addition of procaterol

The mean morning peak expiratory flow rate was 348.5 ± 37.2 L/min 1 week before procaterol treatment

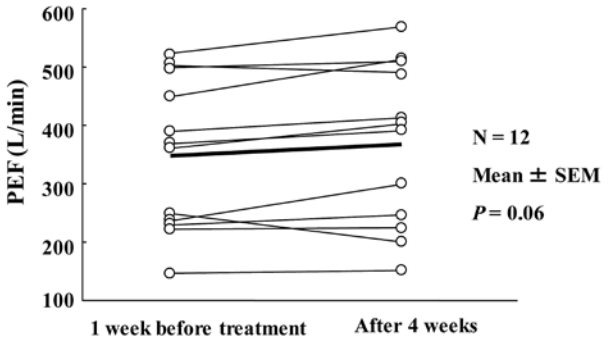

Figure 1 Change in morning peak expiratory flow rates after addition of procaterol (100 μg/day) in patients with bronchial asthma under inhaled corticosteroids

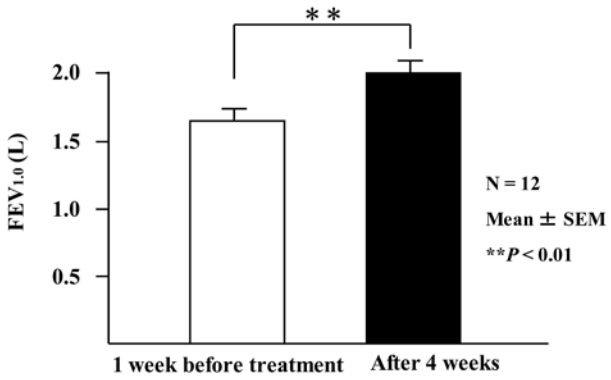

Figure 3 Change in $FEV_{1.0}$ after addition of procaterol (100 μg/day) in patients with bronchial asthma under inhaled corticosteroids

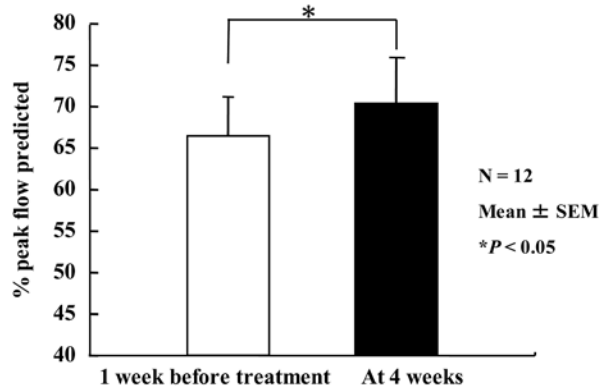

Figure 2 Change in peak expiratory flow expressed as a percentage of the predicted value after addition of procaterol (100 μg/day) in patients with bronchial asthma under inhaled corticosteroids

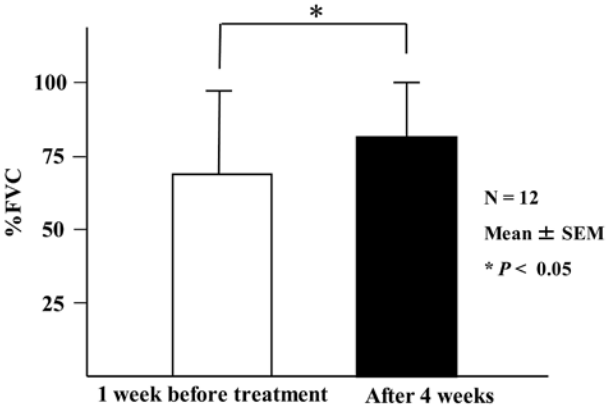

Figure 4 Change in %FVC after addition of procaterol (100 μg/day) in patients with bronchial asthma under inhaled corticosteroids

and 367.8 ± 40.4 L/min at 4 weeks ($P = 0.06$), indicating a tendency toward improvement (Figure 1). The morning peak expiratory flow expressed as a percentage of the predicted value significantly increased to 70.5 ± 5.4 % ($P < 0.05$) after concomitant use of the β_2-agonist compared with the baseline of 66.7 ± 4.6 % (Figure 2). The mean improvement was 5.4 ± 3.1 % ($P = 0.11$).

2. Change in $FEV_{1.0}$

There was a significant improvement in the mean $FEV_{1.0}$ from 1.73 ± 0.20 L a week before treatment to 2.05 ± 0.21 L at 4 weeks ($P < 0.01$) (Figure 3).

3. Change in %FVC

There was an improvement in the mean %FVC from 77.2 ± 8.5 % a week before treatment to 83.5 ± 6.31 % at 4 weeks ($P < 0.05$) (Figure 4).

4. Change in threshold of acetylcholine

The mean threshold of acetylcholine significantly increased from 1275.0 ± 53.0 μg/mL before treatment to 2435.0 ± 234.0 μg/mL at 4 weeks ($P < 0.01$) (Figure 5).

DISCUSSION

Onset of action of β_2-agonists is quicker than other bronchodilators, in particular, inhalers of short-acting β_2-agonists can relax the airway smooth muscle in a

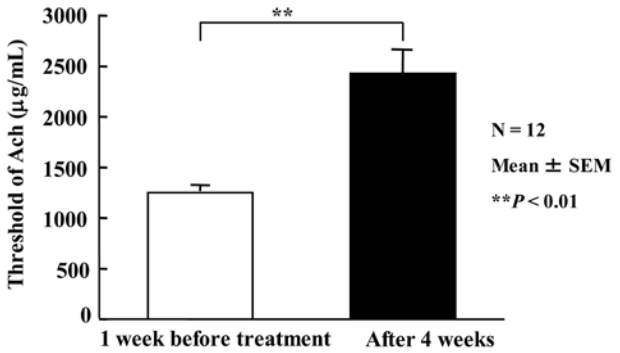

Figure 5 Change in airway hyperresponsiveness (threshold of acetylcholine) after addition of procaterol (100 μg/day) in patients with bronchial asthma under inhaled corticosteroids

few minutes after the drug reached the airways. The drugs bind to β_2-receptors in the airway smooth muscle and activate adenylate cyclase which increases cAMP, resulting in bronchodilation[14]. Inhaled β_2-agonists also enhance ciliary movement, enhances excretion of airway secreta and increase airway clearance[14]. β_2-agonitsts including isoproterenol once provoked an issue of cardiovascular side effects because they also stimulate β_1-receptors to the same extent. Since then, the primary focus of developing β_2-agonists was to improve selectivity for β_2-receptors in order to reduce cardiovascular side effects. Currently available short-acting β_2-agonists have high selectivity for β_2-receptors, proving the problem was almost cleared[14]. Nevertheless, these short-acting β_2-agonists still have other issues to be concerned with. The onset of action is rapid yet the duration of action is short, and their effectiveness as a reliever of asthma attacks has been confirmed, yet it was pointed out that symptoms become destabilized to the extent even leading to asthma deaths because the bronchodilating effect decreases over the long time when they are used on a regular basis, and they enhance airway hyperresponsiveness[4]. In particular, a well known report is a paper revealing association between increased asthma deaths and increased use of short-acting β_2-agonists in New Zealand in 1980s and it was followed by many other reports suggesting relationship between increased asthma deaths and increased use of short-acting β_2-agonists across the world. To overcome this issue, long-acting inhaled β_2-agonists were developed. These new agonists and patch formulations developed in Japan have replaced the conventional short-acting agonists, and their position as a controller has been established[1]. Such a long duration of action can be ascribable to increased liposolubility of side chains of β_2-agonists, which enables longer retention of the drug in tissues[16] and improved sustained release system extended to 12－24 hours for the patch formulation[17]. These long-acting β_2-agonists are effective in relieving symptoms at night and early morning and exercise-induced asthma and in improving QOL. It has been demonstrated that their bronchodilating effect rarely decreases even over a long time[18,19] airway hyperresponsiveness rarely enhances[20] and they have little effect on cardiovascular system[21] However, anti-inflammatory effect of β_2-agonists is too weak to be a cure for asthma in general. Therefore, a combination with anti-inflammatory drugs is essential and various guidelines also place an importance on this point. Given the results of recently published SMART study that even monotherapy of long-acting β_2-agonists increased asthma deaths and the study was terminated[22], anti-inflammatory drugs should be combined. Coadministration of long-acting β_2-agonists as a controller and inhaled steroids or antileukotriene antagonists exhibited superior effect to monotherapy. It is not recommended either to switch from combination of inhaled steroids and β_2-agonists into β_2-agonists monotherapy even after symptoms are well controlled[23,24]. Thus, any β_2-agonist should be combined with inhaled steroids after all. On the other hand, procaterol, clenbuterol, and tulobuterol have high selectivity for β_2-receptors and longer duration of action for 8 to 10 hours than other short-acting β_2-agonits and are recommended as a controller[1].

Unlike inhalants, regular use of oral β_2-agonists over the long time rarely decreases brochodilating effect, enhances hyrereactivity or cause serious adverse effect such as asthma death[2] Moreover, oral β_2-agonists are characterized by much easier use compared to inhalants which require special devices and techniques. It is easy and simple to just swallow tablets for patients with decreased lung function and the elderly patients who have difficulties in inhaling drugs. Compared to patch formulations, oral formulation have some advantages : no need to strip off a thin seal or

they cause no skin reaction on the affected site[25]. Oral formulations are systemic and should not be used in patients with hyperthyroidism. Caution is needed when they are prescribed to patients with underlying cardiovascular disease, hypertension or diabetes[1]. They appear to be useful controllers if these issues are taken care of. In fact, oral β_2-agonists have still been widely used in Japan although there were few studies on the combination of inhaled steroids and oral β_2-agonists. We often experience that oral β_2-agonists are effective in patients whose airway obstructive symptoms cannot be controlled by a moderate to high dose of 800 μg/day beclomethasone as anti-inflammatory therapy. Therefore, we examined the effect of oral procaterol combined with corticosteroids. Oral procaterol improved $FEV_{1.0}$ significantly after combined use. Morning peak flow rate and a peak flow predicted value were improved by approx. 5 % without a significant difference. Probably because there were considerable variations in peak flow rates due to different age and physique and the number of 12 patients is too small to have a significant difference. Overall, there was a tendency toward improvememt and it appeared that a combination was superior to monotherapy of inhaled steroids in patients with morning dip. FVC also improved because occlusive symptoms improved, which suggests increased gas volume inhaled into the whole lungs and a possibility of improving inhalation efficiency by combination with inhaled steroids. It is needed to compare the effect of coadministration of an inhaled steroid with an oral β_2-agonist and combination of a long-acting inhaled β_2-agonist available in other countries and an inhaled steroid. If oral formulations are demonstrated to improve inhalation efficiency through dilation of peripheral airways more than inhalants do, use of oral β_2-agonists will be recommended more without reservation. Further studies are expected. On the other hand, bronchial hypersensitivity appear to be improved given increased threshold of acetylcholine. This can be ascribable to antagonism of procaterol against constriction of the airway smooth muscle. It seems that oral β_2-agonists do not aggravate airway hypersensitivity unlike short-acting β_2-agonists if inhaled steroids are combined. Long-acting β_2-agonists have been demonstrated not to aggravate airway hyperresponsiveness compared to short-acting β_2-agonists[20,26]. There was no significant difference in change in airway hyperresponsiveness in a study between patch and oral formulations of tulobuterol in childhood asthma and it suggests that long-acting β_2-agonists can be used as a controller when being combined with corticosteroids[27]. In this study, oral procaterol combined with inhaled steroids did not aggravate but rather improved airway hyperreactivity. This might be a character of oral procaterol but it is too early to comment on that before the long-term effect of oral procaterol is confirmed. It is safe to say that oral procaterol can be used as a controller because it does not aggravate airway hypersensitivity as short-acting β_2-agonists do. The benefits of oral β_2-agonists distinctive from long-acting β_2-agonists and patch formulations include ease of use and certain bronchodilation of peripheral airways attained by systemic effect of oral medication[28]. It will be necessary to demonstrate that oral β_2-agonists or some of them have significant advantages over inhaled β_2-agonists including combination therapy with inhaled steroids. Oral β_2-agonists require caution to patients with thyroid disease, cardiovascular disesase, diabetes, etc., given the side effects caused by systemic administration, and therefore, it is needed to determine criteria to clarify whom oral β_2-agonists are indicated for. In addition, new oral β_2-agonists should be a once-a-day formulation with a longer duration of action for 12 to 24 hours rathen than the current 8－10 hours and have much fewer cardiovascular side effects, and others such as tremor and headache to be used as a controller.

CONCLUSION

The study suggests that oral β_2-agonists combined with inhaled steroids can improve asthmatic symptoms which are not well controlled by inhaled steroids alone, and be an effective controller like long-acting inhaled β_2-agonists and patch formulations.

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