

Respiratory pathophysiologic responses

Regularly inhaled β -agonists with steroids are not harmful in stable asthma

Matti Heino, MD Vantaa, Finland

Regular use of inhaled β -agonists with steroids was not harmful in stable asthma. Morning and evening peak expiratory flow (PEF) values were recorded daily for 1 week (week 1) before regular inhalation of β -agonists and steroids. Then β -agonists were withdrawn and used as needed for a 2-week washout period. The PEF values of the first week (week 1) were compared with the PEF values before treatment during a further 1-week period (week 4) of as-needed use of β -agonists. The mean evening PEF values were significantly higher (difference = 9.55 L/min; $p = 0.017$; 95% confidence interval [CI], 1.80 to 17.30 L/min), and the mean morning PEF values were nearly significantly higher (difference = 6.49 L/min; $p = 0.088$, 95% CI, -0.99 to 14.00 L/min) during regular β -agonist use. There were significantly more patients with more symptom days, including nights with awakening, during as-needed treatment (difference in ratio of patients = 40.74%; $p = 0.0001$; 95% CI, 20.21% to 61.27%). When nocturnal symptoms are considered separately, there were more patients with more nights with awakening during as-needed treatment with a nearly significant difference (difference in ratio of patients = 12.96%; $p = 0.0654$; 95% CI, 0.92 to 25.00%). PEF monitoring should be used to distinguish the majority of patients with asthma who have higher PEF values during regular treatment from those who do better with administration of β -agonists as needed. To deny patients with asthma regular use of small doses of β -agonists in general is to deny individual differences among patients with asthma. (J ALLERGY CLIN IMMUNOL 1994;93:80-4.)

Key words: Asthma, β -agonist, PEF, steroid, symptoms

Recent recommendations¹ and studies^{2, 3} discourage the regular use of inhaled β -agonists for the treatment of asthma in general. Regularly inhaled β -agonists, even with inhaled steroids, have been reported to result in low peak expiratory flow (PEF) values and increased asthma symptoms.² Whether regular use of inhaled β -agonists is harmful or not is debatable; the problem appears to be inadequate antiinflammatory treatment.⁴⁻⁶

Our clinical practice does not indicate general deterioration of PEF values and symptoms with regular use of inhaled β -agonists and steroids in stable asthma. To test this, 54 patients with asthma undergoing follow-up care were studied.

Abbreviations used

CI:	Confidence interval
PEF:	Peak expiratory flow
FEV ₁ :	Forced expiratory volume in 1 second

METHODS

Patients

Fifty-four consecutive patients with asthma (32 women, 22 men) aged 17 to 70 years with a mean age of 48.72 years, who were receiving follow-up care between May 1992 and March 1993, were included in the study. The months of July and August 1992 were excluded because of pollen seasons that might affect the period of as-needed use of β -agonists. Patients with asthma who had not been able to carry out previous PEF measurements were also excluded. All patients with asthma had shown repeated rises of 15% and 60 L/min in PEF values after use of inhaled β -agonists. The best of three readings from a mini-Wright peak flow meter (Ferraris Medical, Inc., Holland, N.Y.) was used. Thereafter, 51 patients received inhaled beclomethasone dipropionate (mean, 1245 μ g/day; range, 500 [three patients] to 2500 μ g/day), and three received budesonide (800, 1600, 2400 μ g/day) 15 minutes after

From Peijas Hospital, Department of Pulmonary Medicine, Pulmonary Unit, Vantaa, Finland.

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Reprint requests: Matti Heino, MD, Peijas Hospital, Department of Pulmonary Medicine, Sairaalakatu 1, SF-01400 Vantaa, Finland.

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TABLE 1. The mean morning and evening PEF values during regular inhalation of steroids and β -agonists (week 1) compared with regular inhalations of steroids and as-needed use of β -agonists (week 4)

PEF (L/min)	Mean		Difference	<i>p</i> Value*	95% CI†
	Week 1	Week 4			
Morning	448.23	441.75	6.49	0.088	−0.99 to 14.00
Evening	460.22	450.67	9.55	0.017	1.80 to 17.30

*Paired *t* test.

†95% CI of mean difference.

administration of either 0.2 mg of salbutamol (one patient received 0.1 mg) or 0.5 mg of terbutaline (one patient received 1.0 mg) twice a day. Two patients received 0.2 mg of salbutamol four times a day. One patient received 0.2 mg of fenoterol twice a day. A large volume spacer (Volymatic; Glaxo, Ware, U.K.) was used for beclomethasone, salbutamol, and fenoterol inhalations; and a dry powder inhaler (Turbuhaler; GWS Perlos, Kontiolahti, Finland) was used for budesonide and terbutaline. Eight patients also received inhaled anticholinergics and long-acting theophylline tablets alone or in combination throughout the study without any changes. All patients had stable asthma during treatment, with daily variability of PEF values less than 20%.¹ All patients had been receiving inhaled steroids for at least 1 month, and they had regularly inhaled β -agonists (salbutamol, 47 patients; terbutaline, 6 patients; fenoterol, 1 patient) for a mean period of 35.96 weeks (SD = 28.16 weeks) before the study.

Study design

The patients continued their regular treatment. Morning and evening PEF values were recorded for 1 week, before treatment, and 15 minutes after administration of the β -agonist (week 1). Then β -agonists were withdrawn and used only as needed. After a 2-week washout period, morning and evening PEF values were recorded for 1 week (week 4) before and after administration of inhaled steroids (and rescue β -agonists if used). This mimicked the protocol during the first week and kept the observer blinded. A single-blind approach was chosen because this study was an extension of a normal follow-up procedure to introduce β -agonists to be taken only as needed according to new guidelines.¹ The patients would have also easily distinguished the active β -agonist drug from placebo. All weekly recordings were separately coded.

Statistics

The mean morning and evening PEF values before administration of β -agonists were calculated for each patient in weeks 1 and 4. The paired *t* test was used to determine the mean differences between the morning

and evening PEF values of both weeks. Total daily symptoms, as well as nocturnal symptoms separately, were recorded. The patients recorded a symptom day if they had either cough, wheeze, or tightness in the chest one or more times on that day. A symptom night was recorded if the patient was awakened during the night or had tightness in the chest when waking up in the morning. The number of days on which rescue β -agonists were required were also recorded. The sign test was used for the direction of differences in the number of symptom days, symptom nights, and days when β -agonists were used during weeks 1 and 4. Results were statistically significant if the two-tailed *p* value was less than 0.05.

RESULTS

The mean morning and evening PEF values were lower in week 4 than in week 1. The difference was statistically significant for the evening PEF values (*p* = 0.017) and nearly significant for the morning values (*p* = 0.088) (Table I). The patient who received 0.2 mg of salbutamol four times a day in week 1 received 0.2 mg three times a day in week 4 with no use of rescue β -agonists during either week. The other patient who received 0.2 mg of salbutamol four times a day in week 1 used no β -agonists in week 4 or rescue β -agonists in week 1. The evening PEF values for both of these patients were measured 6 hours after the previous dose of β -agonist. Both the morning and evening PEF values of both patients were lower in week 4.

The data on symptoms and use of rescue β -agonists are summarized in Table II. The sign test was appropriate because nine patients had not recorded every symptom day in week 4 when they had more symptom days compared with week 1. In week 1 there were three patients (5.56%) and in week 4, 19 patients (35.19%) who had more rescue β -agonist days compared with the other week. The difference in the ratio of patients (29.63%) in favor of week 1 was statistically

TABLE II. Symptom days and symptom nights and rescue β -agonist days during regular inhalations of steroids and β -agonists (week 1) compared with regular inhalation of steroids and as-needed use of β -agonists (week 4)

	Number of patients with more		
	Symptom days*	Symptom nights	Rescue β -agonist days
In week 1	5	2	3
In week 4	27	9	19
No difference	22 (20)†	43 (42)†	32 (31)†
Gain (%)‡	40.74	12.96	29.63
<i>p</i> Value‡	0.0001	0.0654	0.0009
95% CI§	20.21-61.27	0.92-25.00	12.61-46.65

*Total, includes symptom nights.
†Number of patients with no findings in either week.
‡Difference in ratio of patients in favor of week 1 by sign test.
§95% CI of difference.

significant ($p = 0.0009$). Two patients had the same number of symptom days and 1 rescue β -agonist day in both weeks. There were five patients (9.26%) with more symptom days, including nocturnal symptoms, in week 1 and 27 (50.00%) in week 4. The difference in the ratio of patients (40.74%) was significant ($p = 0.0001$) in favor of week 1. When nocturnal symptoms were considered separately, there were two patients (3.70%) with more symptom nights in week 1 and nine (16.67%) in week 4. The difference in the ratio of patients (12.96%) was nearly significant ($p = 0.0654$) in favor of week 1.

DISCUSSION

This study showed that the regular use of small doses of inhaled β -agonists with a substantial dose of inhaled steroids had no adverse effects on either the morning or evening PEF values in patients with stable asthma. Patients with more symptom days and rescue β -agonist days were more numerous during as-needed use of β -agonists. The use of the sign test (i.e., change in direction instead of quantitative data) apparently underestimated the symptoms and use of rescue β -agonists in week 4, which was the week of symptoms.

There are only a few studies addressing the use of inhaled β -agonists and steroids together compared with steroids alone in asthma. The combined use of β -agonists and steroids was found to be better than steroids alone in reducing bronchial hyperreactivity measured 12 hours after ad-

ministration of the β -agonist.⁷ Shepherd et al.⁸ showed that regular use of β -agonist was superior to as-needed use in reducing symptoms in patients with asthma, most of whom were also using inhaled steroids.

The results of this study are largely in contrast to those of the New Zealand study in which the effects of regular inhalation of fenoterol were compared with effects of as-needed use.² Nevertheless, a common finding in both studies was the significantly higher evening PEF values before regularly inhaled β -agonist doses compared with as-needed use. In the present study the evening PEF values were measured after the morning dose in nearly every patient in week 1. The ratio of patients with more days of rescue β -agonist use was significantly higher in week 4. In the study by Sears et al.² the patients used β -agonists four times a day during regular use. Thus the higher evening PEF values in patients receiving regular treatment in the present study could not be explained by administration of a β -agonist shortly before the measurement, as suggested by Sears et al.²

The lower morning PEF values in the New Zealand study² were attributed to the regular use of β -agonists and their adverse effect on nighttime pulmonary function. In the present study the ratio of patients with more symptom days, including nights with awakening, was significantly higher in week 4 than in week 1. Considered separately, the increase in the ratio of patients with more nights with awakening in week 4 was nearly sta-

tistically significant. Thus regular use of β -agonists did not have an adverse effect on symptoms. Also the morning PEF values were now lower in week 4, though the change was not statistically significant in terms of the p value. In terms of the 95% confidence interval (CI), the increase in the ratio of patients in week 4 with more nocturnal symptoms was 12.96% (95% CI, 0.92 to 25.00%), which could at best be as high as 25%; it would at least be 1%. Because zero was not included in the CI, patients would not fare more poorly when receiving regular treatment compared with as-needed use of β -agonists. Likewise, but now with zero just barely being included in the far end of the CI (95% CI, -0.99 to 14.00 L/min), the mean drop of 6.49 L/min in week 4 in the morning PEF value could be as high as 14 L/min against a meaningless rise of no more than 1 L/min in favor of as-needed use. A rise of 1 L/min in favor of as-needed use of β -agonists could hardly be of any clinical importance. The information given by the CI, not by the arbitrary dichotomous p value alone, is the clinically meaningful estimate of the difference that a treatment can have.^{9, 10} Hence, together with the increase in total symptoms, and nocturnal symptoms separately, this drop in the morning PEF value in week 4 appears to be clinically significant. It should be remembered that the PEF measurement gives the peak of the flow-volume curve compared with the forced expiratory volume in 1 second (FEV₁) measurement that gives more information on the small airways, which may contribute to symptoms. The future use of a small handheld FEV₁ meter for daily lung function measurements would be preferable to the PEF measurement.

The lack of absolute figures in the New Zealand study² makes it impossible to assess the magnitude of the difference in PEF values during regular versus as-needed use of β -agonists. In a recent conference summary⁶ Dr. Sears gave a difference of only 2.5% for the PEF values between the groups in favor of as-needed use of fenoterol. Because the changes were so small, their clinical significance, despite statistical significance, is by no means convincing. Moreover, the changes were of the same magnitude as those in the present study now in favor of regular β -agonist use. In their article Sears et al.² stated in the methods section that they did not evaluate whether those patients receiving inhaled steroids had adequate antiinflammatory medication. No

more than 11 of 50 patients receiving inhaled steroids in their study were prescribed a daily dose of inhaled steroids that exceeded 800 μ g. The lowest daily dose of inhaled steroids was 150 μ g. They concluded that not even inhaled steroids protected patients from the adverse effects of regular use of β -agonists. This may have been the case in their patients, but it hardly holds for other patients receiving more effective antiinflammatory treatment.

In the Saskatchewan study³ the authors were cautious in interpreting the causal relationship between the increased use of β -agonists and asthma morbidity and mortality rates. The end results could have been due to a more severe asthma in those receiving more β -agonists. Also the lack of adequate antiinflammatory treatment was possible.^{3, 6}

As yet, there are no convincing studies showing that small doses of inhaled β -agonists given regularly are harmful when used together with adequate doses of inhaled steroids. On the contrary, this and other similar studies^{7, 8} show that a better control of asthma might be achieved with regular use of inhaled β -agonists and steroids. Besides a more substantial antiinflammatory therapy in the present study, the differences with the New Zealand study² may be related to the dosage of β -agonists. The fact that β -agonists were given regularly, four times a day, in the New Zealand study² and only twice a day in the present study might imply that larger doses of β -agonists could exert an untoward effect that does not appear when smaller doses are used. Small doses of β -agonists alone twice a day for 2 years did not increase bronchial hyperreactivity in patients with asthma,¹¹ in contrast to the New Zealand study² in which larger doses of regularly administered β -agonists resulted in increased hyperreactivity. It should be taken into consideration that there may be yet unidentified subgroups of patients with asthma who may react in different ways to regular or as-needed use of β -agonists. There may be differences among patients with asthma in geographically isolated populations. It has even been suggested that β -receptors may be different among ethnic groups.¹²

In conclusion, this study showed that regular use of inhaled β -agonists together with steroids was not harmful. It was actually beneficial in terms of symptoms and PEF values. The changes in PEF values between as-needed use and use

before regular β -agonist doses were small but reflected the changes in symptoms. It is an oversimplification to regard the regular use of a small dose of β -agonist as always harmful in patients with stable asthma who are well medicated. As our knowledge of asthma increases, we may be able to offer a more flexible tailor-made medication. At present it seems advisable to conduct PEF monitoring in every patient, as outlined in this study, to distinguish the majority who feel better and have better PEF values when receiving regular β -agonist treatment from the minority who do better when β -agonists are used as needed.

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