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EFFECT OF INHALED FORMOTEROL AND BUDESONIDE ON EXACERBATIONS OF ASTHMA

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ABSTRACT

Background The role of long-acting, inhaled β_2 -agonists in treating asthma is uncertain. In a double-blind study, we evaluated the effects of adding inhaled formoterol to both lower and higher doses of the inhaled glucocorticoid budesonide.

Methods After a four-week run-in period of treatment with budesonide (800 μg twice daily), 852 patients being treated with glucocorticoids were randomly assigned to one of four treatments given twice daily by means of a dry-powder inhaler (Turbohaler): 100 μg of budesonide plus placebo, 100 μg of budesonide plus 12 μg of formoterol, 400 μg of budesonide plus placebo, or 400 μg of budesonide plus 12 μg of formoterol. Terbutaline was permitted as needed. Treatment continued for one year; we compared the frequency of exacerbations of asthma, symptoms, and lung function in the four groups. A severe exacerbation was defined by the need for oral glucocorticoids or a decrease in the peak flow to more than 30 percent below the base-line value on two consecutive days.

Results The rates of severe and mild exacerbations were reduced by 26 percent and 40 percent, respectively, when formoterol was added to the lower dose of budesonide. The higher dose of budesonide alone reduced the rates of severe and mild exacerbations by 49 percent and 37 percent, respectively. Patients treated with formoterol and the higher dose of budesonide had the greatest reductions — 63 percent and 62 percent, respectively. Symptoms of asthma and lung function improved with both formoterol and the higher dose of budesonide, but the improvements with formoterol were greater.

Conclusions In patients who have persistent symptoms of asthma despite treatment with inhaled glucocorticoids, the addition of formoterol to budesonide therapy or the use of a higher dose of budesonide may be beneficial. The addition of formoterol to budesonide therapy improves symptoms and lung function without lessening the control of asthma. (N Engl J Med 1997;337:1405-11.)

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INHALED glucocorticoids are considered the first-line treatment for patients with moderate-to-severe, persistent asthma.¹⁻³ However, many patients taking an inhaled glucocorticoid continue to have symptoms and need additional treatment. Inhaled β_2 -agonists are widely used for symptomatic relief in patients with asthma, but their regular use has been the subject of recent controversy.⁴⁻⁶ Treatment with the long-acting, inhaled β_2 -agonists formoterol and salmeterol provides better control of symptoms and improves lung function more than short-acting β_2 -agonists.^{7,8} Combining a long-acting, inhaled β_2 -agonist with an inhaled glucocorticoid led to a greater improvement in the control of symptoms and in lung function than doubling the dose of the inhaled glucocorticoid.^{9,10} However, some studies have suggested that long-term treatment with long-acting, inhaled β_2 -agonists might result in tolerance to its effects or mask an increase in airway inflammation.¹¹⁻²⁰

We studied the hypothesis that the addition of regular treatment with the long-acting, inhaled β_2 -agonist formoterol to a lower or higher dose of the inhaled glucocorticoid budesonide would result in improved control of symptoms and lung function, without any long-term deterioration in the control of asthma over a 12-month period. The primary outcomes evaluated were the rates of severe and mild

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*The members of the study group are listed in the Appendix.

exacerbations of asthma. Secondary outcomes included lung function, symptoms, and the need for β_2 -agonists for rescue therapy.

METHODS

Patients

Patients 18 to 70 years old, who had had asthma for at least six months and had been treated with an inhaled glucocorticoid for at least three months were enrolled. The forced expiratory volume in one second (FEV_1) at base line had to be at least 50 percent of the predicted value,²¹ with an increase of at least 15 percent in FEV_1 from the base-line value after the inhalation of 1 mg of terbutaline. Patients taking more than 2000 μg of beclomethasone or 1600 μg of budesonide daily by pressurized metered-dose inhaler, 800 μg of budesonide daily by Turbuhaler dry-powder inhaler (Astra, Södertälje, Sweden), or 800 μg of fluticasone daily were excluded. They were also excluded if they had had three or more courses of oral glucocorticoids or had been hospitalized for asthma during the previous six months.

Study Design

The study was a double-blind, randomized, parallel-group study with four treatment groups. It was carried out at 71 centers in nine countries (Belgium, Canada, the Netherlands, Israel, Italy, Luxembourg, Norway, Spain, and the United Kingdom). Approval from regulatory agencies and ethics committees was obtained in all countries and at all centers. All patients gave witnessed oral or written informed consent.

The study had a 4-week run-in period, followed by 12 months of randomized treatment. There were nine scheduled visits to the clinic: at the start of the run-in period, at the start of treatment, and after 2 weeks and 1, 2, 3, 6, 9, and 12 months of treatment. In addition, telephone contacts were scheduled with the patients after 2 weeks of the run-in period, after 2 to 5 days of treatment, and after 4, 5, 7, 8, 10, and 11 months of treatment.

All patients entering the run-in phase received inhaled budesonide (Pulmicort, Astra Draco, Lund, Sweden) at a dose of 800 μg twice daily (total daily dose, 1600 μg), plus 250 μg of inhaled terbutaline (Bricanyl, Astra Draco) as needed. At the end of the run-in period, patients were eligible for randomization if they had complied with the run-in treatment and had stable asthma. Compliance was defined as the use of 75 to 125 percent of the recommended number of doses of inhaled budesonide, as indicated on a hidden mechanical counter built into the dry-powder inhaler that could be read only by the investigators. Asthma was defined as stable if none of the following occurred during the last 10 days of the run-in period: diurnal variation of more than 20 percent in the peak expiratory flow on 2 consecutive days; use of four or more inhalations of β_2 -agonist per day on 2 consecutive days; awakening due to asthma on 2 consecutive nights; or the need to use oral glucocorticoids.

Eligible patients were randomly assigned to receive one of the following treatments (each dose was given twice daily) for a period of 12 months: 100 μg of budesonide (total daily dose, 200 μg) plus placebo; 100 μg of budesonide plus 12 μg of formoterol (Oxis, Astra Draco; total daily dose, 24 μg); 400 μg of budesonide (total daily dose, 800 μg) plus placebo; or 400 μg of budesonide plus 12 μg of formoterol. Terbutaline (250 μg per inhalation) was used as rescue medication. All medications were inhaled by means of a multidose Turbuhaler. The stated doses of budesonide, formoterol, and terbutaline are the metered doses. The patients were randomly assigned to treatment groups in balanced blocks of four at each center.

Outcome Measures

Exacerbations of Asthma

The primary outcomes studied were the rates of severe and mild exacerbations of asthma per patient per year. A severe exacer-

beration was defined as one requiring treatment with oral glucocorticoids, as judged by the investigator, or a decrease in the peak expiratory flow as measured in the morning to more than 30 percent below the base-line value on two consecutive days. Seventy-three percent of severe exacerbations were identified clinically by the investigators. The base-line peak expiratory flow was defined as the mean peak expiratory flow in the morning during the last 10 days of the run-in period. All severe exacerbations had to be treated with a 10-day course of oral glucocorticoids (30 mg of prednisolone or prednisone or 24 mg of methylprednisolone per day). Patients who had three severe exacerbations within three months or a total of five severe exacerbations were withdrawn from the study. Days with mild exacerbations were defined as days when one of the following occurred: a peak expiratory flow in the morning that was more than 20 percent below the base-line value; the use of more than three additional inhalations of terbutaline per 24 hours as compared with the base-line period; or awakening at night due to asthma. Single, isolated days of mild exacerbations were not counted. The base-line value was the mean value for the variable during the last 10 days of the run-in period. Days included in a severe exacerbation were excluded from the count of days with mild exacerbations.

Diary-Card Data

Patients filled in a daily diary during the run-in and treatment periods, recording the best of three measurements of peak expiratory flow made with a Vitalograph Peak Flow Meter (Vitalograph, Buckingham, United Kingdom) in the morning and evening before medication; symptoms of asthma during the night or the daytime (according to a 4-point scale, with 0 indicating no symptoms and 3 incapacitating symptoms); awakening due to asthma; use of inhalations of terbutaline for rescue therapy (at night or during the day); and the use of oral glucocorticoids.

Clinic Visits

At scheduled clinic visits, clinical measures, adverse events, withdrawals, or changes in medication were recorded, diary cards were reviewed, and FEV_1 was measured.

Episode-free Days

An episode-free day was defined as a day with optimally controlled asthma — that is, no need for rescue therapy with inhaled β_2 -agonists, an asthma-symptom score of 0, a morning peak expiratory flow that was 80 percent or more of the base-line value, and no adverse events.

Statistical Analysis

The data analysis followed a factorial design, and pairwise comparisons were made by appropriate contrasts. Rates of exacerbation were analyzed by applying a Poisson regression model. Other variables were analyzed with use of analysis of covariance, with base-line variables as covariates. For data from the diaries, mean values for the last 10 days before each visit were used. The analysis included all randomized patients (intention-to-treat approach). Data for patients who withdrew or discontinued therapy were included up to the time of their withdrawal. The number of days when treatment was received was entered as a covariate.

RESULTS

From April 1994 to April 1995, consecutive potentially eligible patients were identified at the participating institutions. Of the 1114 patients entering the run-in period, 262 were excluded before randomization because they were determined to be ineligible. The remaining 852 patients (436 women and 416 men) were randomly assigned to treatment

groups. Base-line demographic and spirometric characteristics and diary-card data are presented in Table 1. The differences in base-line data among the groups were minor and nonsignificant. Of the 852 patients randomly assigned to receive treatment, 694 (81 percent) completed the 12-month study. Of the 158 patients who did not complete the study, 44 did not fulfill the entry criteria and were incorrectly randomized, 30 had worsening of asthma, 29 had adverse events, and 55 left the study for other reasons (13 because of noncompliance with study procedures, 5 because they intended to become pregnant, 5 because they relocated, 20 for personal reasons, and 12 because they were lost to follow-up). Most of the incorrectly randomized patients were withdrawn in the initial part of the study after a visit to the clinic for monitoring. Only three remained in the study for more than 90 days.

Exacerbations of Asthma

Table 2 shows the two primary outcome variables, the rate of severe exacerbations and the rate of mild exacerbations, according to treatment group. The lowest rates were among the patients who received the higher dose of budesonide plus formoterol. There was no significant interaction between budesonide

and formoterol in terms of either severe or mild exacerbations. Formoterol and the higher dose of budesonide produced additive reductions in severe and mild exacerbations.

The rate of severe exacerbations was reduced by 26 percent when formoterol was added to the lower dose of budesonide and by 49 percent when the higher dose of budesonide was given alone. The combination of formoterol and the higher dose of budesonide reduced the estimated rate of severe exacerbations by 63 percent, from 0.91 per year per patient to 0.34 ($P < 0.001$). Giving the higher dose of budesonide resulted in a greater reduction in the rate of severe exacerbations than did the addition of formoterol ($P = 0.03$). Altogether, 80.8 percent of the patients receiving both formoterol and the higher dose of budesonide were free of severe exacerbations during the study, as compared with 61.4 percent of the patients receiving the lower dose of budesonide without formoterol. Of the 30 patients who left the study because their asthma worsened, 21 were withdrawn because they had frequent severe exacerbations: 10 receiving the lower dose of budesonide alone, 7 receiving the lower dose of budesonide plus formoterol, 4 receiving only the higher dose of budesonide, and none receiving the higher

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.*

CHARACTERISTIC	LOWER-DOSE BUDESONIDE PLUS PLACEBO (N=213)	LOWER-DOSE BUDESONIDE PLUS FORMOTEROL (N=210)	HIGHER-DOSE BUDESONIDE PLUS PLACEBO (N=214)	HIGHER-DOSE BUDESONIDE PLUS FORMOTEROL (N=215)
Sex (M/F)	108/105	104/106	102/112	102/113
Age (yr)				
Mean	42	41	44	42
Range	18-70	18-68	18-70	17-70
Dose of inhaled steroids at start of run-in period ($\mu\text{g}/\text{day}$)				
Mean	823	821	818	856
Range	100-2000	150-2000	100-2000	100-2000
Symptom score during the day at end of run-in period†				
Mean	0.50	0.52	0.49	0.52
Range	0-2.00	0-2.10	0-2.60	0-2.30
Symptom score at night at end of run-in period†				
Mean	0.30	0.27	0.26	0.29
Range	0-2.11	0-2.00	0-2.10	0-2.20
FEV ₁ at start of run-in period				
Liters	2.53	2.50	2.38	2.48
% of predicted value	75.8	75.7	75.4	76.3
PEF at end of run-in period (liters/min)				
Morning	397	399	381	394
Evening	402	402	387	402

*The lower dose of budesonide was 100 μg given twice a day (total, 200 μg per day); the higher dose was 400 μg twice a day (total, 800 μg per day). Formoterol was given at a dose of 12 μg twice a day (total, 24 μg). FEV₁ denotes forced expiratory volume in one second, and PEF peak expiratory flow.

†Symptoms were scored from 0 (no symptoms) to 3 (very severe symptoms interfering with activity or sleep).

TABLE 2. CLINICAL OUTCOMES.*

VARIABLE	LOWER-DOSE BUDESONIDE PLUS PLACEBO	LOWER-DOSE BUDESONIDE PLUS FORMOTEROL	HIGHER-DOSE BUDESONIDE PLUS PLACEBO	HIGHER-DOSE BUDESONIDE PLUS FORMOTEROL	P VALUE	
					FORMOTEROL VS. PLACEBO	LOWER VS. HIGHER DOSE OF BUDESONIDE
Exacerbations (no.)						
Severe	153	125	90	57		
Mild	5953	3980	4289	2241		
Patients withdrawn from study because of severe exacerbations (no.)	10	7	4	0		
Estimated yearly rate of exacerbations (no./patient/yr)						
Severe	0.91	0.67	0.46	0.34	0.01	<0.001
Mild	35.4	21.3	22.3	13.4	<0.001	<0.001
Patients without severe exacerbation (%)	61.4	70.3	71.8	80.8		
Episode-free days (mean % of year)†	41.7	51.1	45.7	54.8	0.001	0.16
Mean values at end of study						
Symptom score at night‡	0.37	0.31	0.38	0.20	<0.001	0.08
Symptom score during the day‡	0.57	0.46	0.53	0.33	<0.001	0.01
Rescue medication at night (no. of inhalations)	0.29	0.18	0.20	0.11	<0.001	0.003
Rescue medication during the day (no. of inhalations)	0.91	0.57	0.82	0.44	<0.001	0.08
Awakenings (no./night)	0.14	0.11	0.10	0.05	0.03	0.003

*The lower dose of budesonide was 100 μg given twice a day (total, 200 μg per day); the higher dose was 400 μg twice a day (total, 800 μg per day). Formoterol was given at a dose of 12 μg twice a day (total, 24 μg).

†Episode-free days were defined as days with no symptoms, no use of rescue medication, and a peak expiratory flow more than 80 percent of the base-line value.

‡Symptoms were scored from 0 (no symptoms) to 3 (very severe symptoms interfering with activity or sleep).

dose of budesonide plus formoterol ($P=0.01$ for the difference among the treatment groups).

The rate of mild exacerbations was reduced by 37 percent when the higher dose of budesonide, rather than the lower dose, was given and by 40 percent when formoterol was added to the lower dose of budesonide. The combination of budesonide and the higher dose of formoterol reduced the estimated rate of mild exacerbations by 62 percent, from 35.4 per patient per year to 13.4 ($P<0.001$). There was no significant change in the rate of severe or mild exacerbations in any treatment group during the course of the study.

Symptoms

At the end of the run-in period, when patients received 800 μg of budesonide twice a day, clinical-symptom scores, the rate of use of rescue medication, and the frequency of nighttime awakening were low in all four groups (Table 1). The addition of formoterol to budesonide therapy was associated with a significant further improvement in both daytime and nighttime symptom scores (Table 2). The higher dose of budesonide was significantly better than the lower dose in controlling symptoms during the day, but patients in both treatment groups that received budesonide without formoterol had a slight

increase in symptom scores as compared with the run-in period.

The need for rescue medication was reduced significantly by adding formoterol, during both the day and the night, and by the use of the higher dose of budesonide, during the night but not during the day. The addition of formoterol to budesonide therapy was associated with a significantly increased number of episode-free days; the higher dose of budesonide was not associated with a significant increase (Table 2).

Lung Function

FEV₁ increased significantly in all groups during the run-in period and increased further with the addition of formoterol (Fig. 1). The higher dose of budesonide was associated with a significantly higher FEV₁ than the lower dose. Peak expiratory flow in the morning and evening increased considerably when formoterol was added (Fig. 2). The higher dose of budesonide was associated with a significant increase in peak expiratory flow, although less than that associated with the addition of formoterol.

In the formoterol groups, the peak expiratory flow in the morning was higher during the first days of treatment than subsequently (i.e., after day 3; $P<0.001$). For the rest of the 12-month treat-

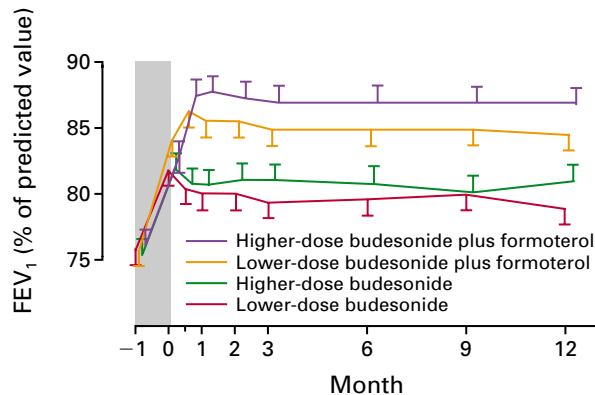


Figure 1. Forced Expiratory Volume in One Second (FEV₁) during the Study.

FEV₁ is shown as a mean percentage of the predicted value during the run-in period (shaded area) and the treatment period. The bars indicate 2 SE. During the run-in period, all patients received 800 μ g of budesonide twice daily. Patients were then randomly assigned to twice-daily treatment with 100 μ g of budesonide, 100 μ g of budesonide plus 12 μ g of formoterol, 400 μ g of budesonide, or 400 μ g of budesonide plus 12 μ g of formoterol.

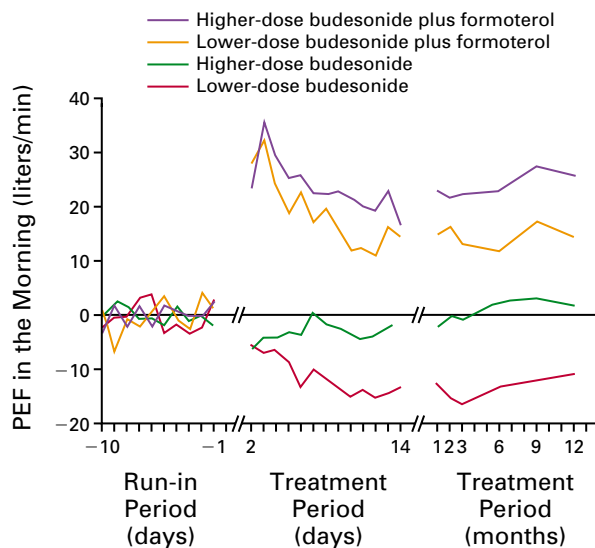


Figure 2. Changes in Mean Peak Expiratory Flow (PEF) in the Morning during the Run-in Period, on Days 1 through 14 of Treatment, and at Months 1 through 12 of Treatment.

During the run-in period all patients received 800 μ g of budesonide twice daily. Patients were then randomly assigned to twice-daily treatment with 100 μ g of budesonide, 100 μ g of budesonide plus 12 μ g of formoterol, 400 μ g of budesonide, or 400 μ g of budesonide plus 12 μ g of formoterol.

ment period, the peak expiratory flow remained stable and considerably higher than the value in the groups treated with budesonide alone (Fig. 2).

Adverse Events

All treatments were well tolerated throughout the study. The proportion of patients reporting adverse events was similar in the four treatment groups. Eleven patients were hospitalized because of asthma: three receiving the lower dose of budesonide plus placebo, one receiving the lower dose of budesonide plus formoterol, five receiving the higher dose of budesonide plus placebo, and two receiving the higher dose of budesonide plus formoterol. Twenty-nine patients withdrew because of adverse events: six receiving lower-dose budesonide plus placebo, six receiving lower-dose budesonide plus formoterol, eight receiving higher-dose budesonide plus placebo, and nine receiving higher-dose budesonide plus formoterol. Seven withdrawals were due to pharmacologically predictable adverse events: three in the group receiving lower-dose budesonide plus formoterol (one with headache and two with tremor) and four in the group receiving higher-dose budesonide plus formoterol (two with tremor, one with tachycardia, and one with oral candidiasis). The other 22 withdrawals were due to throat irritation (2 patients), gastrointestinal effects (5), and miscellaneous side effects (15).

DISCUSSION

We examined the hypothesis that adding regular treatment with the long-acting inhaled β_2 -agonist formoterol to therapy with the inhaled glucocorticoid budesonide would improve symptoms of asthma without a long-term worsening of the disease, as indicated by the rates of severe and mild exacerbations. We found no evidence of deterioration in the control of asthma over the course of a year when formoterol was added to budesonide therapy. In fact, the addition of formoterol decreased the incidence of both severe and mild exacerbations. This effect was independent of the dose of budesonide. The rates of severe and mild exacerbations were also lower among the patients given the higher dose of budesonide; this effect was independent of the addition of formoterol. For severe exacerbations, the effect of the higher dose of budesonide was significantly more pronounced than the effect of formoterol.

Regular treatment with long-acting, inhaled β_2 -agonists has not been shown to modify chronic airway inflammation in patients with asthma.^{22,23} The reason for the reduction in the rate of severe exacerbations with formoterol is not clear. Possible explanations include an inhibitory effect on the acute inflammatory changes that occur during a severe exacerbation; an inhibitory effect on airway smooth-

muscle contraction, plasma extravasation, or both — assuming that these are important to the development of severe acute exacerbations; and an increased deposition of budesonide in the airways after the inhalation of formoterol. Acute exacerbations of asthma are associated with an influx of eosinophils, neutrophils, or both.^{24,25} Formoterol has been shown to inhibit the influx of inflammatory cells in animal models of acute airway inflammation.²⁶ Formoterol is a potent functional antagonist of airway smooth-muscle stimulants and inhibits plasma extravasation.²⁷⁻³⁰

In our study, the addition of formoterol to either the lower or the higher dose of budesonide also improved asthma-symptom scores and lung function and reduced the need for rescue medications. The improvement in the control of symptoms is in agreement with the results of other studies, which have shown better control of symptoms when long-acting, inhaled β_2 -agonists are added to the treatment regimen.^{7-10,31,32}

The control of asthma symptoms and lung function were better in the higher-dose budesonide groups than in the lower-dose groups, although the effect of increasing the dose of budesonide on these measures was less marked than that of adding formoterol. The relative effects of adding formoterol or giving a higher dose of budesonide on the control of symptoms and on lung function in this study are in keeping with observations made with salmeterol.^{9,10}

Regular treatment with formoterol combined with budesonide did not cause any long-term loss of control of asthma. There were no signs of worsening of disease or tolerance to the effects of medication with regard to any clinical or functional variable examined, except for a decrease in the effect of formoterol on peak expiratory flow in the morning after the first two days of treatment. The addition of formoterol resulted in a substantial increase in peak expiratory flow in the morning during the first one to two days of treatment, followed by a slight decrease in both budesonide groups. The peak expiratory flow then remained stable and significantly higher than in the budesonide-only groups for the rest of the one-year study period. One possible explanation is the development of limited tolerance to the bronchodilating effect of formoterol during the early phase of regular treatment, as demonstrated in other studies.^{11-16,18,19} Our findings suggest that such tolerance has little or no clinical significance.

It is important to emphasize that our conclusions may apply only when formoterol is given with an inhaled glucocorticoid.³³ Another limitation of our study is that patients underwent randomization only if they had stable asthma during the last 10 days of the run-in period, when all patients were treated with 1600 μg of budesonide daily. This is a relatively high dose of budesonide, considering that inhala-

tion from a Turbuhaler delivers twice as much budesonide to the airways as inhalation from pressurized metered-dose inhalers.^{34,35}

Our results support therapeutic guidelines that recommend the addition of a long-acting inhaled β_2 -agonist to low doses of inhaled glucocorticoids in patients with persistent symptoms of asthma or less than optimal lung function.³ Increasing the maintenance dose of inhaled glucocorticoids might be a more appropriate initial therapeutic step in patients with repeated severe exacerbations of asthma.

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APPENDIX

The following physicians, listed according to country, enrolled patients: Belgium — W. DeBacker, M. Decramer, P.-M. Mingeot, L. Siemons, J. Verhaert, and W. Vincken; Canada — M. Alexander, J. Bouchard, A. Day, A. Knight, J.-L. Malo, D. Marciniuk, J.G. Martin, S. Peters, B. Sanders, B. Sproule, and D. Stubbings; the Netherlands — A. Baas, T.A. Bantje, J. Creemers, H. Sinnighe Damsté, W. Evers, S. Gans, A. Greefhorst, H. Hassing, F. Maesen, M.J. Möllers, H.R. Pasma, Z. Pelikan, P.E. Postmus, J. Prins, B.M. Santana, M. Schrijver, A.P. Sips, R. Stallaert, L. van der Maas, and A.J. van Harrevelde; Israel — J. Greif, D. Heimer, A.H. Rubini, and A. Wollner; Italy — F. Bariffi, F. Bonifazi, V. Brusasco, G. D'Amato, L. Fabbri, C. Franco, L. Gandola, C. Giuntini, E. Gramiccioni, V. Grassi, L. Marazzini, A. Rossi, A.M. Santolicandro, and C. Sturani; Luxembourg — J.-P. Parini; Norway — L. Bjermer and N. Ringdal; Spain — J.L. Alvarez Sala, P.L. Cabrera Navarro, S. Romero, J. Sanchis, V. Sobradillo, and H. Vereá; United Kingdom — G. Basran, L.M. Campbell, D. Franklin, G.J. Gibson, R.C. Joshi, A. Knox, A.B. MacLean, R. Scott, R. Smith, A. Tattersfield, and J.P. Vernon. The following Astra employees were involved in the study: C.-A. Bauer (project leader), M. Best (data entry), C. Hultquist (medical advisor), F. Jackson (safety evaluation), A. Lennon (medical coordinator), S. Lindgren (safety evaluation), H. MacFarlane (computing), A. McLean (deputy project leader), M. Nevinson (medical coordinator), M.-Å. Persson (computing), and K. Svensson (statistician). The national medical monitors were: F. Bellemans, T. Ben-Or, S. Bordonaro, M. Chiesa, I. Garcia, J. Haddon, S. Holthe, M. Huybrechts, A. Ning, H. Rijskamp, F. Stafford, and M. van den Dobbelen.

REFERENCES

1. Haahtela T, Järvinen M, Kava T, et al. Comparison of a β_2 -agonist, terbutaline, with an inhaled corticosteroid, budesonide, in newly detected asthma. *N Engl J Med* 1991;325:388-92.
2. van Essen-Zandvliet EE, Hughes MD, Waalkens HJ, Duiverman EJ, Poock SJ, Kerrebijn KF. Effects of 22 months of treatment with inhaled corticosteroids and/or beta-2-agonists on lung function, airway responsiveness, and symptoms in children with asthma. *Am Rev Respir Dis* 1992;146:547-54.
3. Global Initiative for Asthma. Global strategy for asthma management and prevention. Washington, D.C.: National Heart, Lung, and Blood Institute, 1995. (Publication no. 95-3659.)
4. Sears MR, Taylor DR, Print CG, et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;336:1391-6.
5. Spitzer WO, Suissa S, Ernst P, et al. The use of β -agonists and the risk of death and near death from asthma. *N Engl J Med* 1992;326:501-6.
6. Drazen JM, Israel E, Boushey HA, et al. Comparison of regularly scheduled with as-needed use of albuterol in mild asthma. *N Engl J Med* 1996;335:841-7.
7. Pearlman DS, Chervinsky P, LaForce C, et al. A comparison of salmeterol with albuterol in the treatment of mild-to-moderate asthma. *N Engl J Med* 1992;327:1420-5.
8. Kesten S, Chapman KR, Broder I, et al. A three-month comparison of twice daily inhaled formoterol versus four times daily inhaled albuterol in the management of stable asthma. *Am Rev Respir Dis* 1991;144:622-5.
9. Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994;344:219-24.
10. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroids. *Am J Respir Crit Care Med* 1996;153:1481-8.

11. Kalra S, Swystun VA, Bhagat R, Cockcroft DW. Inhaled corticosteroids do not prevent the development of tolerance to the bronchoprotective effect of salmeterol. *Chest* 1996;109:953-6.
12. Bhagat R, Kalra S, Swystun VA, Cockcroft DW. Rapid onset of tolerance to the bronchoprotective effect of salmeterol. *Chest* 1995;108:1235-9. [Erratum, *Chest* 1996;109:592.]
13. Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ. Long-term effects of a long-acting β_2 -adrenoceptor agonist, salmeterol, on airway hyperresponsiveness in patients with mild asthma. *N Engl J Med* 1992;327:1198-203.
14. Ramage L, Lipworth BJ, Ingram CG, Cree IA, Dhillon DP. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. *Respir Med* 1994;88:363-8.
15. Newnham DM, McDevitt DG, Lipworth BJ. Bronchodilator subsensitivity after chronic dosing with formoterol in patients with asthma. *Am J Med* 1994;97:29-37.
16. O'Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled β_2 -agonists in asthma. *N Engl J Med* 1992;327:1204-8.
17. Tattersfield AE. Clinical pharmacology of long-acting beta-receptor agonists. *Life Sci* 1993;52:2161-9.
18. Cockcroft DW, Swystun VA, Bhagat R. Interaction of inhaled beta 2 agonist and inhaled corticosteroid on airway responsiveness to allergen and methacholine. *Am J Respir Crit Care Med* 1995;152:1485-9.
19. Yates DH, Sussman HS, Shaw MJ, Barnes PJ, Chung KF. Regular formoterol treatment in mild asthma: effect on bronchial responsiveness during and after treatment. *Am J Respir Crit Care Med* 1995;152:1170-4.
20. Lofdahl CG, Svedmyr N. Beta-agonists — friends or foes? *Eur Respir J* 1991;4:1161-5.
21. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows: report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal: official statement of the European Respiratory Society. *Eur Respir J* 1993;6:Suppl 16:5-40.
22. Roberts JA, Bradding P, Walls AF, et al. The influence of salmeterol xinafoate on mucosal inflammation in asthma. *Am Rev Respir Dis* 1992;145:Suppl:A418. abstract.
23. Gardiner PV, Ward C, Booth H, Allison A, Hendrick DJ, Walters EH. Effect of eight weeks of treatment with salmeterol on bronchoalveolar lavage inflammatory indices in asthmatics. *Am J Respir Crit Care Med* 1994;150:1006-11.
24. Turner MO, Hussack P, Sears MR, Dolovich J, Hargreave FE. Exacerbations of asthma without sputum eosinophilia. *Thorax* 1995;50:1057-61.
25. Fahy JV, Kim KW, Liu J, Boushey HA. Prominent neutrophilic inflammation in sputum from subjects with asthma exacerbation. *J Allergy Clin Immunol* 1995;95:843-52.
26. Whelan CJ, Johnson M, Vardey CJ. Comparison of the anti-inflammatory properties of formoterol, salbutamol and salmeterol in guinea-pig skin and lung. *Br J Pharmacol* 1993;110:613-8.
27. Erjefalt I, Persson CG. Long duration and high potency of antiexudative effects of formoterol in guinea-pig tracheobronchial airways. *Am Rev Respir Dis* 1991;144:788-91.
28. Advenier C, Qian Y, Koune JD, Molimard M, Candenas ML, Naline E. Formoterol and salbutamol inhibit bradykinin- and histamine-induced airway microvascular leakage in guinea-pig. *Br J Pharmacol* 1992;105:792-8.
29. Baluk P, McDonald DM. The beta 2-adrenergic receptor agonist formoterol reduces microvascular leakage by inhibiting endothelial gap formation. *Am J Physiol* 1994;266:L461-L468.
30. Kallstrom BL, Sjoberg J, Waldeck B. The interaction between salmeterol and beta 2-adrenoceptor agonists with higher efficacy on guinea-pig trachea and human bronchus in vitro. *Br J Pharmacol* 1994;113:687-92.
31. Britton MG, Earnshaw JS, Palmer JBD. A twelve month comparison of salmeterol with salbutamol in asthmatic patients. *Eur Respir J* 1992;5:1062-7. [Erratum, *Eur Respir J* 1993;6:150.]
32. Kesten S, Chapman KR, Broder I, et al. Sustained improvement in asthma with long-term use of formoterol fumarate. *Ann Allergy* 1992;69:415-20.
33. Verberne AAPH, Frost C, Roorda RJ, van der Laag H, Kerrebijn KF, Dutch Paediatric Asthma Study Group. One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med* 1997;156:688-95.
34. Thorsson L, Edsbacker S, Conradson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. *Eur Respir J* 1994;7:1839-44.
35. Borgstrom L, Derom E, Stahl E, Wahlin-Boll E, Pauwels R. The inhalation device influences lung deposition and bronchodilating effect of terbutaline. *Am J Respir Crit Care Med* 1996;153:1636-40.

CORRECTION

Effect of Inhaled Formoterol and Budesonide on Exacerbations of Asthma

Effect of Inhaled Formoterol and Budesonide on Exacerbations of Asthma . On page 1408, the sentence that begins in line seven of the left-hand column should have read, "The combination of formoterol and the higher dose of budesonide reduced . . .," not "The combination of budesonide and the higher dose of formoterol reduced . . .," as printed. We regret the error.