

Brief communications

Salmeterol does not cause tolerance during long-term asthma therapy

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Controversy regarding tolerance to β_2 -agonist asthma therapy has surfaced periodically over the past 20 years, and recently it has again become a focus of attention. Although there is evidence that tolerance develops to the nonpulmonary effects of β_2 -agonist,^{1,2} there is still uncertainty among many clinicians who treat patients with asthma as to whether any clinically significant tolerance develops to the pulmonary effects of these drugs, particularly to the recently introduced long-acting β_2 -agonist salmeterol.

This report, which represents results from the largest database of patients receiving salmeterol in clinical studies in the United States, supports the growing body of evidence that patients with asthma do not show any loss of bronchodilator effect after regular exposure to β_2 -agonist,³⁻⁸ although some loss of the bronchoprotective effect has been reported in a few exercise-induced bronchospasm and methacholine challenge studies.^{6,9}

METHODS

Study design

Four randomized, multicenter, double-blind, placebo-controlled, parallel-group studies were conducted in patients with reversible mild-to-moderate asthma (FEV₁ of 50% to 80% of predicted value after medication was withheld); two of the studies ($n = 556$), identically designed, evaluated salmeterol aerosol from a pressurized metered-dose inhaler (pMDI)^{7,8}; whereas the other two identically designed studies ($n = 451$) evaluated salmeterol powder, inhaled from a dry powder device (DPI).¹⁰ All patients provided written informed consent, and the study protocols were approved by institutional review boards at each center.

Patients were treated with one of the following for 12 weeks: salmeterol aerosol, 42 μ g (actuated dose) twice

Abbreviations used

AUC:	Area under the curve
DPI:	Dry powder device
PEF:	Peak expiratory flow
pMDI:	Pressurized metered-dose inhaler

daily by pMDI or salmeterol powder, 50 μ g (blister content) by DPI twice daily through a breath-activated device (DISKHALER,* Glaxo Wellcome); albuterol aerosol, 180 μ g four times daily (by pMDI); or placebo. All patients could also use albuterol pMDI as needed for acute symptoms, except 8 hours before and on clinic days during pulmonary function testing. Inhaled corticosteroids or cromolyn could also be used, provided that the dosage regimen was held constant throughout the study. Theophylline and oral β -agonists were not permitted during these trials.

Patients were seen in the clinic every 2 weeks during the treatment phase. On the first day of treatment and after 4, 8, and 12 weeks of treatment, FEV₁ was measured at least every hour over a 12-hour period after the morning dose of study drug was given. Patients self-measured peak expiratory flow (PEF) every morning before their first dose of study drug and every evening before the last dose of study drug. Patients also recorded daily, on diary cards, the number of times they were awakened by asthma symptoms and the number of puffs of albuterol required each 24 hours.

Statistical analysis

For the purpose of these analyses, data from the two identical salmeterol pMDI studies were combined, as were the data from the two identical salmeterol DPI studies. Area under the curve (AUC) was defined as the area in liter-hours between the 12-hour serial FEV₁ curve and a horizontal line corresponding to the treatment day 1 baseline value. Probability (p) values for comparisons of day 1 and week 12 FEV₁ values were based on analysis of variance F-tests. Within-treatment comparisons of change from the beginning to the end of treatment for morning PEF (predicted value), nighttime

From Glaxo Wellcome Inc., Research Triangle Park, N.C.

Supported by Glaxo Wellcome Inc.

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J Allergy Clin Immunol 1996;98:1116-9.

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0091-6749/96 \$5.00 + 0 1/54/76106

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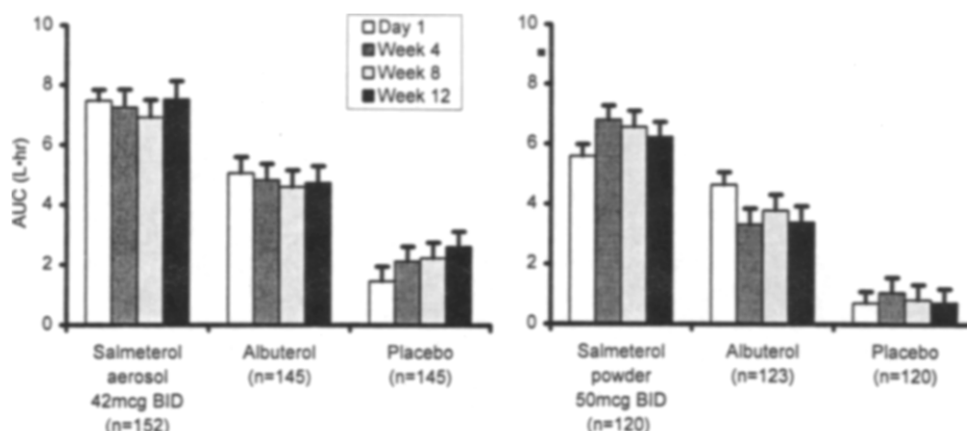


FIG. 1. Mean AUC for FEV₁ (L · hour ± SEM). Only data from patients who completed all four clinic visits and did not receive albuterol within 8 hours of pulmonary function testing were included. BID, Twice daily.

awakenings, and albuterol use were based on a Wilcoxon signed-rank test. A *p* value of 0.05 was considered statistically significant.

RESULTS

There were no statistically significant differences between the mean AUC for FEV₁ on the first day of treatment and after 12 weeks of treatment in either the salmeterol pMDI or DPI group, indicating no loss of bronchodilating effect over time (Fig. 1). Although there were statistically significant changes between the day 1 AUC and week 12 AUC in the albuterol and placebo groups (i.e., a decrease in the albuterol group in the DPI studies only and an increase in the placebo group in the pMDI studies only), there was no consistent pattern of tolerance.

Morning PEF improved only in the salmeterol group in both the DPI and pMDI studies (mean change: 33 and 25 L/min, respectively, with salmeterol; 0 and -10 L/min, respectively, with albuterol; and 1 and -1 L/min, respectively, with placebo; *p* < 0.05). Over the 12 weeks of treatment, there was no statistically significant change in the response to therapy within any of the treatment groups. The least variation in morning PEF occurred in patients who received salmeterol (mean changes: 0.4 L/min in both the DPI and pMDI studies compared with 5.9 and 1.0 L/min with albuterol and 2.9 and 8.1 L/min with placebo in the DPI and pMDI studies, respectively).

Asthma exacerbations (defined as a worsening of asthma that required treatment in addition to study drug, concomitant antiasthma therapy and

rescue albuterol allowed by protocol) occurred least frequently in patients who received salmeterol (50 exacerbations), and exacerbations were evenly distributed throughout the 12 weeks of treatment (Fig. 2). Exacerbations in patients who received albuterol (70 exacerbations) or placebo (60 exacerbations) were similarly distributed. Concurrent inhaled corticosteroid use did not appear to have an impact on the asthma exacerbation rate in the salmeterol and albuterol groups (Table I), because approximately one third (salmeterol 30%, albuterol 36%) of the patients used concurrent inhaled corticosteroids, and approximately one third of the exacerbations occurred in patients using inhaled corticosteroids. In the placebo group, the exacerbation rate (47%) was higher than the concurrent steroid use (35%), perhaps because patients received β_2 -agonist therapy only in response to asthma symptoms, rather than prophylactically.

Lastly, analyses of trends within each treatment group showed no evidence of tolerance as measured by changes in nighttime awakenings caused by asthma symptoms or the use of supplemental albuterol over 12 weeks of therapy.

DISCUSSION

These results from a large sample of patients who received either salmeterol pMDI or DPI over a 12-week period clearly demonstrate that there is no tolerance to the bronchodilating properties of salmeterol, confirming the findings of other long-term studies of salmeterol in the maintenance treatment of asthma.^{11, 12} This information, along

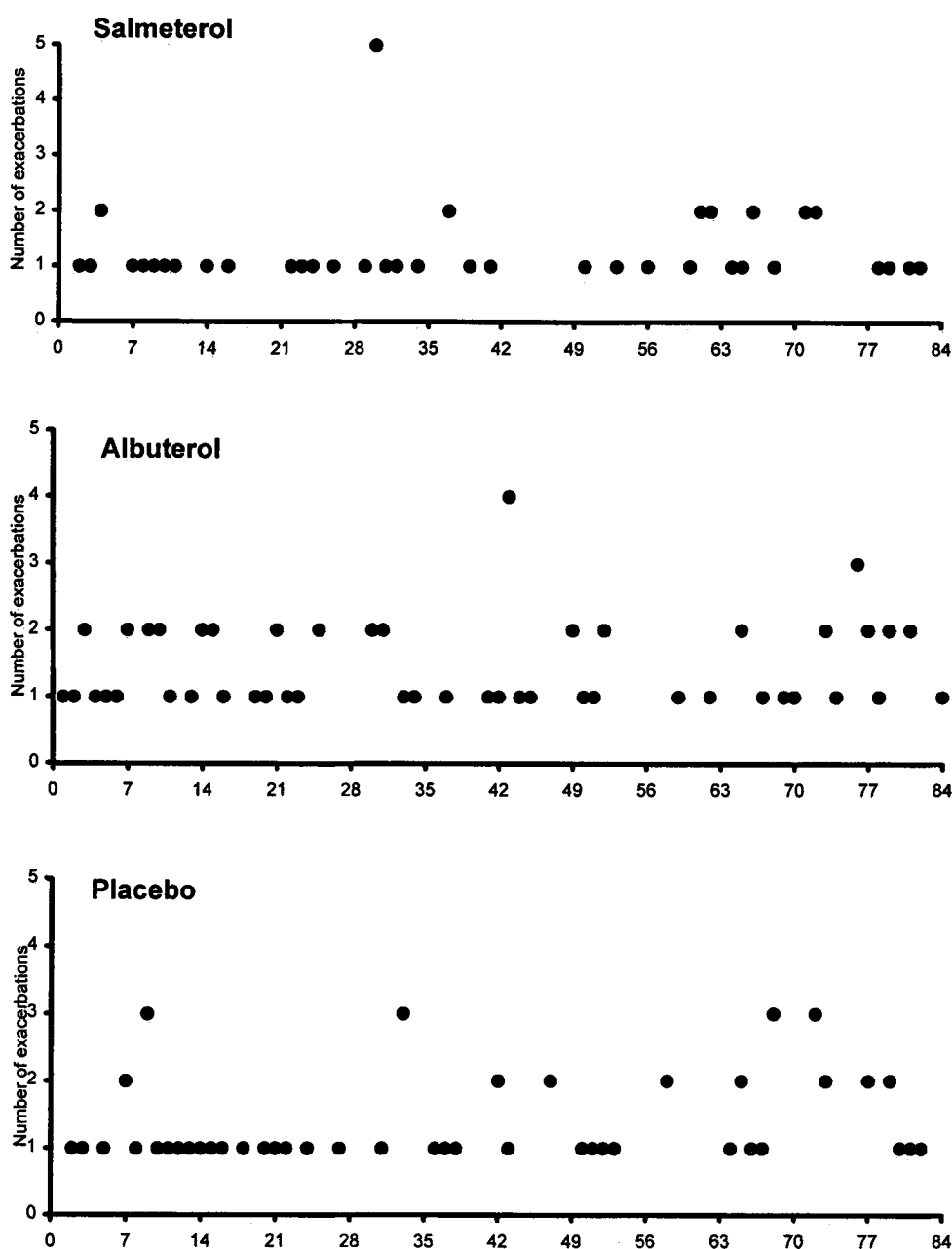


FIG. 2. Days from beginning of treatment to exacerbation, occurring during continuous daily treatment with salmeterol. Excludes exacerbations occurring during clinic visits when supplemental albuterol was withheld as part of the protocol.

with data showing that patients receiving salmeterol by pMDI over 12 weeks who had an asthma exacerbation and were then treated with nebulized albuterol were able to achieve significant bronchodilation regardless of how long they had been receiving salmeterol,¹³ provides further reassurance to clinicians that there is no loss or diminu-

tion of asthma control with salmeterol during long-term use.

These analyses evaluated clinically relevant end points appropriate for charting the effectiveness of a maintenance therapy over an extended period. Responses to provocative challenges with nonspecific stimuli were not measured in these studies.

TABLE 1. Asthma exacerbation data

	Salmeterol (pMDI and DPI)	Albuterol	Placebo
Number of patients with exacerbations	50	49	55
Number of patients using concurrent inhaled steroids with exacerbations	18	17	26

However, had a clinically relevant increase in airway responsiveness occurred in these patients, it would have been reflected most likely in the number of asthma exacerbations, the use of rescue medication, and the number of nighttime awakenings.^{14, 15} In fact, every efficacy variable examined in these studies, including AUC for 12-hour serial FEV₁ (which reflects both magnitude and duration of the bronchodilator response) and PEF, confirmed that maintenance therapy with salmeterol does not produce tolerance to its bronchodilating effects.

We thank Rose Mills for writing assistance.

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