Salmeterol Compared with Current Therapies in Chronic Asthma

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BACKGROUND. Therapy with salmeterol, a long-acting, selective, inhaled β_2-adrenergic agonist, is effective and safe for patients with persistent asthma; however, few long-term studies comparing salmeterol with current combination treatment regimens have been reported.

METHODS. A multicenter, randomized, placebo-controlled, double-blind study was conducted in 386 patients over 41 to 46 weeks in 27 medical centers (two thirds of the investigators were primary care physicians). Patients were randomized to receive either salmeterol or placebo, and further randomized to weaning or nonweaning from current asthma therapies (except inhaled corticosteroids). Treatment groups were: salmeterol/weaning (S + W), placebo/weaning (P + W), salmeterol/no weaning (S + NW), and placebo/no weaning (P + NW). Attempts at active weaning were carried out at the discretion of the investigator for 2 to 6 weeks. Pulmonary function, albuterol use, and asthma symptoms were measured.

RESULTS. The clinical benefits of salmeterol occurred despite weaning off existing nonsteroidal asthma medications. The mean morning peak expiratory flow rate was significantly increased in the S + W group (32.3 L/min) compared with both the P + W (4.9 L/min) and P + NW (6.8 L/min) groups ($P < .001$). Compared with the P + W and P + NW groups, the S + W group experienced significant ($P < .05$) improvements in overall mean asthma symptom scores, mean number of puffs of supplemental albuterol, the percentage of days with no supplemental albuterol use, and the mean number of awakenings caused by asthma (except for the P + NW comparison, $P=.090$). No significant differences were noted between treatment groups in any safety evaluation, including 12-lead electrocardiograms.

CONCLUSIONS. The addition of salmeterol in the treatment of persistent asthma resulted in sustained improvement in pulmonary function and symptoms. The long-term use of salmeterol is safe and improves the clinical course and stability of asthma following reductions in nonsteroidal asthma therapy.

KEY WORDS. Adrenergic B-agonist; asthma; bronchodilator; salmeterol [non-MeSH]. *(J Fam Pract 1998; 47:278-284)*

Asthma is a common illness among children and adults that has a significantly detrimental impact on their lives. Approximately 5% of the US population are affected by asthma, and the incidence is increasing.[1-3]

Guidelines for the treatment of chronic persistent asthma have been developed by various professional groups.[4-8] All advocate the use of anti-inflammatory agents, such as inhaled or oral corticosteroids, to mitigate the underlying disease process. In addition to corticosteroids, many patients use aerosol or oral β_2-agonists, theophylline, leukotriene antagonists, or sodium cromolyn to provide relief of asthma symptoms. However, because there are few comparative data available from clinical trials with which to compare different asthma medications, regimens used in clinical practice reflect regional variations and physicians' personal prescribing habits.

Salmeterol xinafoate is a long-acting, highly selective, β_2-adrenergic agonist that provides up to 12 hours of bronchodilation, approximately twice that of its shorter-acting analogue, albuterol.[9-12] Comparative clinical trials have shown that maintenance therapy with salmeterol (42 µg) twice daily is more effective than albuterol (180 µg) administered four times daily, or only as needed in improving respiratory function and reducing asthma symptoms, in patients with mild-to-moderate asthma while maintaining a comparable safety profile.[9-11] This is the first long-term study (41 to 46 weeks) conducted in the United States to evaluate the efficacy and safety of salmeterol aerosol compared with current asthma therapy.

Given the prolonged duration of bronchodilation and the superior nocturnal asthma symptom-control afforded

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by salmeterol as opposed to other bronchodilators, it has been suggested that twice-daily salmeterol maintenance therapy may allow patients to discontinue use of some of their existing asthma medications, excluding inhaled corticosteroids.[9,10,13,14]

This long-term study, conducted mostly in the primary care setting, was designed to further evaluate the efficacy and safety of salmeterol (42 µg twice daily) in the context of either maintenance or reduction of current asthma medications. The duration of this study was designed to examine the durability of benefits observed with salmeterol therapy.

METHODS

PATIENTS

Men and women at least 12 years of age with asthma (defined by the American Thoracic Society criteria[15,16]) for 6 months or more and who required treatment with at least two routine prescription asthma medications, not including inhaled corticosteroids, were eligible for study participation. After withholding all bronchodilator medications, all patients were to have a baseline forced expiratory volume in 1 second (FEV_1) between 50% and 80% of predicted values and reversibility of airway obstruction demonstrated by a ≥15% increase in baseline FEV_1 within 15 minutes after inhalation of 2 puffs (180 µg) of albuterol. Patients treated with inhaled corticosteroids, sodium cromolyn, or theophylline regimens were to have received the same regimen for ≥30 days before baseline evaluation. Patients taking theophylline were also to have documentation of a steady-state theophylline serum concentration between 5 and 15 µg/mL within 30 days of the screening visit.

Patients were excluded from the study if they had a history of life-threatening asthma, required ≥2 canisters of inhaled β_2-agonist per month, received an oral or parenteral corticosteroid within 30 days of study entry, or were judged by their physician to be clinically unsuitable to undergo weaning off current asthma medications. Excluded from the study were patients with upper or lower respiratory tract infection within 4 weeks of entry, evidence of past or present tuberculosis, a 10-pack per year or longer history of cigarette smoking, a history of any tobacco product use in the last year, recent antibiotic treatment within 2 weeks of entry, significant concurrent disease, or clinical laboratory or electrocardiogram (ECG) abnormality. In addition, patients receiving beta-blockers, digitalis, phenothiazines, polycyclic antidepressants, or macrolide antibiotics were not considered for study participation. Women were excluded if they were premenarchal, pregnant or lactating, or of childbearing potential and not using an acceptable form of birth control. Informed written consent was obtained from all study participants. This study was approved by a governing institutional review board.

STUDY DESIGN AND PROCEDURES

This multicenter, randomized, placebo-controlled, double-blind, parallel-group study was performed in the United States. The study was divided into four phases: (1) a 1- to 2-week run-in phase; (2) a 2-week randomization phase; (3) a 2- to 6-week weaning phase; and (4) a 36-week maintenance phase.

The screening evaluation included a routine physical examination and laboratory tests. Baseline pulmonary function tests (FEV_1) and response to inhaled albuterol (if not documented within the preceding 12 months) were also performed. Eligible patients entered a 1- to 2-week run-in phase during which they continued treatment with their usual asthma medications. Supplemental albuterol inhalation was permitted throughout the study.

Patients recorded the following data on daily diary cards: peak expiratory flow rate, measured before taking asthma medications immediately upon rising in the morning (AM PEF) and immediately before bedtime (PM PEF); self-assessed asthma symptoms; use of asthma medications, including supplemental albuterol inhalation; and nocturnal awakenings due to asthma. Patients measured PEF rates using a hand-held spirometer that met or exceeded American Thoracic Society minimum performance criteria.[24] The greatest value of three attempts was recorded. Asthma symptoms, including chest tightness, shortness of breath, wheezing, and coughing, were rated on a 6-point scale from 0 (no symptoms) to 5 (symptoms severe enough to prevent participation in work, school, or other daily activities).

Patients who complied with study procedures and demonstrated stable asthma symptoms during the run-in phase were randomized to placebo or salmeterol xinafoate (Serevent, Glaxo Wellcome Inc, Research Triangle Park, NC). After 2 weeks in this randomization phase, patients were further randomized either to attempt weaning from nonsteroidal medications or to not attempt weaning. The resulting four treatment groups were 42 µg twice daily (2 puffs) salmeterol plus weaning (S + W); twice daily placebo plus weaning (P + W); salmeterol plus no weaning (S + NW); and placebo plus no weaning (P + NW). The S + NW arm was for blinding purposes only, and only a minimal number of patients were randomized to this arm. Study medication was self-administered following the AM PEF rate measurement and at bedtime following the PM PEF rate measurement.

Weaning from nonsteroidal asthma medications in patients randomized to the S + W and P + W groups began at the third study visit after 2 weeks of double-blind treatment; however, no standardized methods for weaning were instituted. Investigators were instructed to discontinue or taper the dose of one or more of the patient's current asthma medications at their discretion if the diary cards provided evidence of relative asthma stability and compliance with the study procedures. Two additional study visits at 2-week intervals were permitted as needed for further attempts at weaning.

TABLE 1

Patient Demographics and Baseline Characteristics

	Treatment Group			
	P + W (n = 121)	S + W (n = 117)	P + NW (n = 123)	S + NW (n = 25)
Mean age, years (range)	35.1 (12-86)	38.4 (13-85)	34.6 (12-72)	35.9 (12-62)
Sex				
Female, no. (%)	58 (48)	58 (50)	55 (45)	12 (48)
Male, no. (%)	63 (52)	59 (50)	68 (55)	13 (52)
Mean baseline FEV_1				
Before bronchodilation, liters (SE)	2.40 (0.09)	2.38 (0.08)	2.43 (0.07)	2.04 (0.15)
After bronchodilation, liters (SE)	3.00 (0.12)	2.99 (0.11)	2.99 (0.10)	2.60 (0.26)
Reversibility, % (SE)	34 (2)	34 (2)	36 (2)	43 (6)
Percent predicted, % (SE)	68 (2)	66 (2)	67 (2)	61 (4)
Baseline Asthma Medications				
Bronchodilators, no. (%)	121 (100)	116 (>99)	122 (>99)	25 (100)
Albuterol (inhaled and oral), no. (%)	110 (91)	109 (93)	116 (94)	24 (96)
Theophylline, no. (%)	93 (77)	90 (77)	92 (75)	18 (72)
Corticosteroids, no. (%)	84 (69)	81 (69)	78 (63)	16 (64)
Inhaled, no. (%)	77 (64)	75 (64)	75 (61)	14 (56)
Sodium cromoglycate, no. (%)	22 (18)	29 (25)	27 (22)	5 (20)
Nedocromil sodium, no. (%)	12 (10)	13 (11)	16 (13)	2 (8)
Anticholinergic agents, no. (%)	5 (4)	6 (5)	8 (7)	1 (4)

P denotes placebo; W, weaning; S, salmeterol; NW, no weaning; FEV_1, forced expiratory volume at 1 second; SE, standard error.

At the completion of the weaning phase, patients entered a 36-week maintenance phase. While weaning was not attempted during this phase, investigators were permitted to discontinue, add, or adjust the dose of current asthma medications as deemed necessary for optimum control of the patient's condition. Patients were evaluated at 6- to 8-week intervals during this phase.

Two weeks of data were recorded on each individual diary card. Vital signs, adverse events, pulmonary auscultation, and a theophylline level (in the event of an increase in theophylline dose) were obtained at each study visit. In addition, a 12-lead ECG, clinical laboratory tests, a pregnancy test, and a complete physical examination were repeated 12 weeks into the maintenance phase and at the conclusion of the study.

Statistical Methods

Randomization was performed in blocks of 5:5:5:1 for the P + W, S + W, P + NW, and S + NW groups, respectively. The S + NW treatment group was established for blinding purposes only and no statistical analyses were performed on efficacy data from these patients. All analyses were performed on the intention-to-treat population and controlled for investigator effect (ie, terms for investigators were included in the statistical models to adjust for site-to-site differences). The primary efficacy variables were the daily measures of PEF rate.

Mean changes from baseline in PEF data were compared using analysis of variance F tests. Changes from baseline in the individual and composite symptom scores, nocturnal awakenings, and supplemental albuterol use were compared using the nonparametric van Elteren test.[17] Differences in the proportion of patients with asthma exacerbations were assessed using the Fisher exact test.

Baseline and demographic variables were compared using either analysis of variance (for age, height, weight, and pulmonary function tests), a Cochran-Mantel-Haenszel test (for sex and ethnic origin), or the Fisher exact test (for asthma medication use). Differences in ECG data and adverse events were compared for determination of safety using the Fisher exact test. All *P* values were based on two-sided tests of significance at the ≤.05 level.

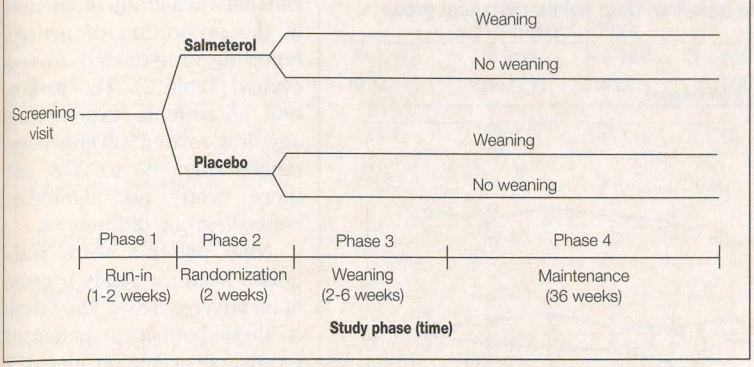
RESULTS

Patient Demographics

Demographic and baseline characteristics are presented in Table 1. A total of 386 patients were enrolled at 27 medical centers (20 primary care physicians enrolled 137 patients and 13 allergy specialists enrolled 249 patients in this study). Within each treatment group, 91% to 96% of patients were using albuterol, 72% to 77% of patients were using theophylline, 18% to 25% were using sodium cromo-

FIGURE 1

Study schema



glycate, 8% to 13% were using nedocromil sodium, and 4% to 7% were using anticholinergic agents. Inhaled corticosteroids were being used by 56% to 64% of patients in each treatment group. Seventy-five patients withdrew from the study; there were no significant differences in the rate of withdrawals among treatment groups. The majority of patients who withdrew (61) did so because of protocol violations, failure to return, or miscellaneous administrative reasons. Five patients were withdrawn because of lack of efficacy.

Peak Expiratory Flow Rate

A significant treatment benefit in the AM PEF rate was achieved with salmeterol therapy and was maintained throughout the study period to produce a significant overall improvement compared with placebo ($P < .001$), regardless of whether the patients were weaned or not weaned (Figure 1). The overall mean increase from baseline in AM PEF rate was 32.3 L/min in S + W group, 4.9 L/min in the P + W group, and 6.8 L/min in the P + NW group. With respect to PM PEF rate, a significant treatment benefit was achieved with salmeterol therapy and maintained throughout the study period, compared with the P + W group ($P = .001$), but not compared with the P + NW group ($P = .058$). The mean increase from baseline in PM PEF rate was 16.1 L/min in the S + W group, 6.6 L/min in the P + NW group, and 0.9 L/min in the P + W group. Over the course of the study, the diurnal variation in PEF was also reduced significantly in the S + W group compared with both placebo groups ($P < .001$). The overall reduction from baseline in diurnal variation PEF was 17.4 L/min in the S + W group, 1.1 L/min in P + NW group, and 3.2 L/min in the P + W group.

Daily Self-Rated Symptoms

All patient-rated asthma symptom scores for shortness of breath, chest tightness, coughing, and wheezing were fairly similar among treatment groups at baseline; however, patients in the S + W group reported significantly lower scores for wheezing, shortness of breath, and chest tightness ($P = .035$, .049, and .012, respectively) than those in the P + NW group. Mean symptom scores for all individual symptoms and the composite symptom score declined after randomization in all treatment groups. Compared with the P + W and P + NW groups, patients in the S + W group experienced a significant improvement from baseline in chest tightness ($P = .032$ and .018, respectively), shortness of breath ($P = .017$ and .036, respectively) and overall symptoms ($P = .040$ and .041, respectively).

Supplemental Albuterol Use

At baseline, the mean number of puffs of supplemental albuterol ranged from 4.2 to 4.8 puffs per day; the percentage of days with no supplemental albuterol use ranged from 7% to 10%. Mean daily use of rescue albuterol decreased and the percentage of albuterol-free days increased in all treatment groups. The S + W group, however, experienced a significantly greater decrease in albuterol use compared with both placebo groups. The mean percentage of days with no supplemental albuterol was significantly higher in the S + W group (48.3%) compared with the P + W group (30.5% ; $P=.004$) and P + NW group (16.1%; $P < .001$). Similarly, the mean number of puffs of albuterol decreased over the study period by 2.34 puffs per day in the S + W group, compared with 1.15 and 0.63 puffs per day in the P + W ($P=.002$) and P + NW ($P < .001$) groups, respectively.

Nighttime Awakenings Caused by Asthma

At baseline, the mean number of awakenings per night caused by asthma ranged from 0.37 to 0.44; the percentage of nights with no awakenings ranged from 66.9% to 72.2%. The mean percentage of nights with no awakenings was significantly higher in the S + W group (91.7%) compared with the P + W group (80.5%; $P=.027$) but not with the P + NW group (78.3%; $P=.090$). Over the study period, the mean number of awakenings was 0.11 in the S + W group compared with 0.26 in the P + W group ($P=.039$) and 0.29 in the P + NW group ($P = .104$).

Weaning

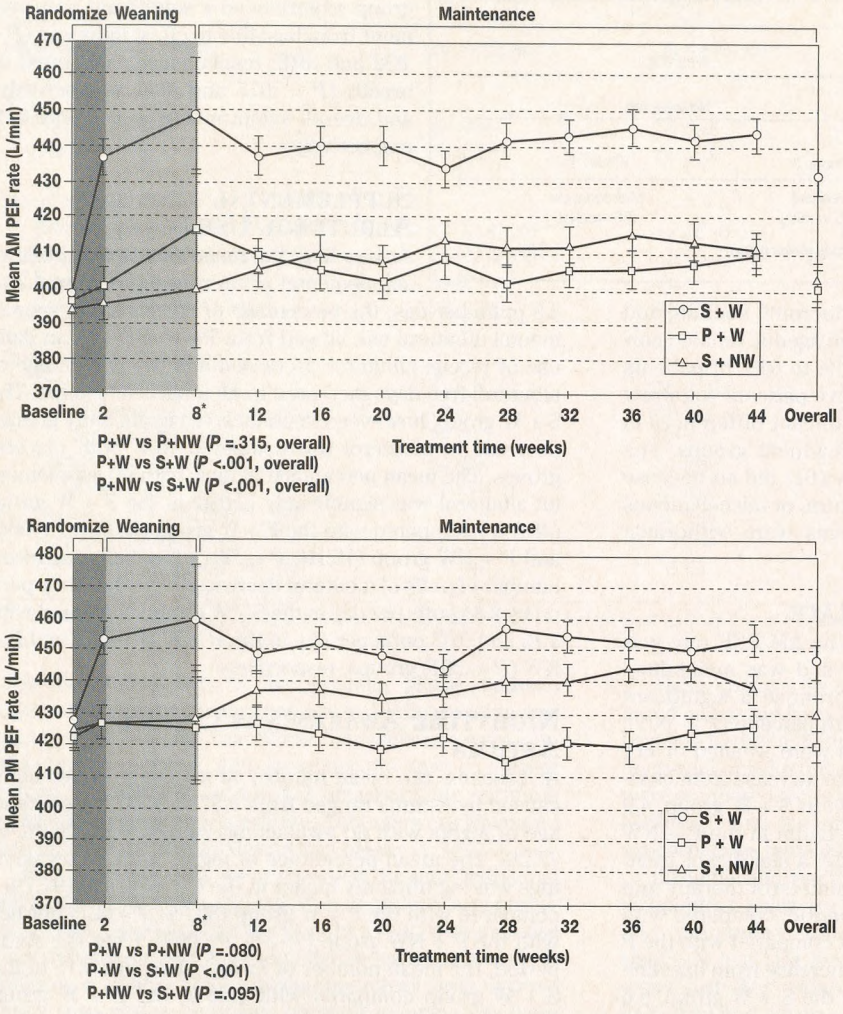
In the S + W group, 62% of patients were successfully weaned from at least one current nonsteroidal asthma medication, compared with 54% of patients in the P + W group. Successful and sustained weaning from at least two nonsteroidal asthma medications was achieved in 11% of patients in the S + W group and in 7% of patients in the P + W group. These differences were not statistically significant.

Asthma Exacerbations

Asthma exacerbations, defined as events requiring treatment in addition to current asthma therapy, the

FIGURE 2

Mean morning (A) and evening (B) peak expiratory flow (PEF) rate. *P* values are based on analysis of variance F tests on change from baseline. Data points represent group means ± SE.



***The 4-week data point for the P + NW group was carried forward and plotted as an 8-week data point.**

P denotes placebo; W, weaning; S, salmeterol; NW, no weaning; SE, standard error of the mean.

study drug, or supplemental albuterol, occurred with similar frequency in each study group. The proportion of patients who experienced exacerbations ranged from 27% to 35%. Analyses of time to first asthma exacerbation and the care setting used for treatment of an asthma exacerbation (eg, home, inpatient hospitalization, emergency department, physician's office, and so forth) also showed no treatment-related differences.

Adverse Events

Overall, there were no significant between-group differences in the proportion of patients reporting drug-related adverse events (Table 2). The proportion of patients experiencing any drug-related adverse event ranged from 9% to 20%, and there were no significant between-group differences.

Nine patients were withdrawn from the study because of an adverse event. Only three of these patients experienced an adverse event considered by the investigator to be possibly, probably, or almost certainly related to the study drugs. One patient receiving placebo experienced coughing, and one other patient experienced palpitations, depression, irritability, and mood swings. One patient treated with salmeterol experienced tremor, nervousness, and nausea. All adverse events resolved once the patients discontinued use of the study drug. No deaths or serious drug-related adverse events occurred.

DISCUSSION

This study demonstrated that salmeterol-treated patients with persistent asthma who attempted to be weaned from current medications improved over baseline, compared with placebo-treated patients in both the weaning and no weaning groups. The benefits associated with salmeterol in this study occurred rapidly after its initiation and were maintained for up to 46 weeks of salmeterol therapy. The improvements in asthma observed in the salmeterol-treated group were noted in all efficacy variables. The salmeterol-treated group had long-term improvement superior to both placebo groups. It may not be surprising that the salmeterol-treated group improved more than the placebo group that attempted weaning from medication (P + W). The salmeterol-treated group, however, showed superior long-term asthma control even over the placebo-treated group that did not attempt to wean any baseline

TABLE 2

Drug-Related Adverse Events

Event	Treatment Group P + W (n=121)	S + W (n=117)	P + NW (n=123)	S + NW (n=25)
Any event, no. (%)	11 (9)	12 (10)	14 (11)	5 (20)
Headache, no. (%)	3 (2)	3 (3)	2 (2)	1 (4)
Sleep disturbance, no. (%)	1 (<1)	2 (2)	0	1 (4)
Tremors, no. (%)	1 (<1)	2 (2)	1 (<1)	0
Nervousness, no. (%)	1 (<1)	2 (2)	1 (<1)	0
Chest tightness, no. (%)	2 (2)	0	0	1 (4)
Inhalation complication, no. (%)	2 (2)	0	0	0
Nausea, no. (%)	0	2 (2)	0	0
Heartburn, no. (%)	0	0	2 (2)	0
Oral symptoms, no. (%)	0	0	0	1 (4)

Note: Table includes adverse events ≥2%.
P denotes placebo; W, weaning; S, salmeterol; NW, no weaning.

nonsteroidal medications (P + NW). These data suggest that patients with persistent asthma may benefit to a greater degree from salmeterol therapy than from other nonsteroidal asthma medications (eg, theophylline, cromolyn, nedocromil).

No between-group differences were observed in the number of asthma exacerbations or the time to the first such episode, indicating that exacerbations occurred at random and were not related to the study drug. Furthermore, treatment with salmeterol over the course of nearly 1 year did not contribute to any adverse effects on vital signs, ECG, or any other physiologic variable.

CONCLUSIONS

These results confirm the efficacy and safety profile established for salmeterol in previous short-term (≤12 weeks) studies, which compared salmeterol with albuterol, theophylline, terbutaline, disodium cromoglycate, and higher dose inhaled corticosteroids.[9,11-13,18-21] These data also confirm the experience from clinical trials that demonstrated the efficacy and safety of salmeterol therapy for periods of up to 1 year.[10,22] Therefore, maintenance therapy with salmeterol can improve pulmonary function and asthma symptoms without compromising safety, even when patients reduce their use of other nonsteroidal asthma medications.

In a similarly designed European study by Charpin and colleagues,[23] patients with chronic asthma requiring maintenance therapy for 2 to 5 years were randomized to either maintain their current medications or receive salmeterol aerosol (42 µg twice daily) while aggressively reducing their use of other asthma medications (S + W arm). At enrollment, 90% of all patients used at least three different drugs. Over the course of this 12-week trial, however, all patients in the S + W arm either discontinued or markedly reduced their existing medications (excluding inhaled corticosteroids) and experienced greater control of their disease compared with the control group.

Our study was designed in part to address the issue of reduction of nonsteroidal medications in the context of long-term salmeterol therapy and to extend the findings of Charpin and colleagues[23] suggesting that salmeterol therapy may be a viable alternative to multidrug regimens in patients with persistent asthma. In our study, although only 62% of patients in the S + W group were successfully weaned from at least one nonsteroidal asthma medication, compared with 54% of patients in the P + W group, those salmeterol-treated patients who were weaned continued to experience significant improvements in pulmonary function and asthma symptoms compared with the P + W group. The most important explanation of this finding is that the present study did not employ an asthma medication reduction algorithm (ie, investigators tapered or discontinued medications regimens at their discretion). In this study, weaning was not aggressively controlled, and the extent of weaning was not a major study objective; therefore, it is not surprising that greater degrees of weaning were not achieved. The results of the present study together with those reported by Charpin and colleagues suggest that patients with persistent asthma may be successfully maintained with salmeterol plus inhaled corticosteroids in place of multidrug regimens.

In conclusion, the addition of salmeterol in the treatment of persistent asthma resulted in improvement in pulmonary function and asthma symptoms that persisted for 41 to 46 weeks. The benefits of salmeterol occurred despite the patient's weaning from existing asthma medications, suggesting that salmeterol can be an effective addition to inhaled corticosteroids and may be an effective alternative to current multidrug regimens for some asthma patients. The most current asthma guidelines state, "Gain control as quickly as possible; then decrease treatment to the least medication necessary to maintain control."[24]

When compared with current asthma medication regimens, the step-down treatment to salmeterol and the long-term use of salmeterol improves the clinical course and stability of asthma while permitting reductions in nonsteroidal medications without compromising safety.

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REFERENCES

1. Sly RM. Mortality from asthma, 1979-1984. J Allergy Clin Immunol 1988; 82:705-17.
2. Weiss KB, Wagener DK. Changing patterns of asthma mortality. Identifying target populations at high risk. JAMA 1990; 264:1633-7.
3. Gergen DJ, Weiss KB. Changing patterns of asthma hospitalization among children: 1979 to 1987. JAMA 1990; 264:1688-92.
4. International consensus report on diagnosis and management of asthma. Bethesda, Md: National Heart, Lung, and Blood Institute, 1992. US Department of Health and Human Services publication No. 92-3091.
5. Expert Panel on the Management of Asthma. Guidelines for the diagnosis and management of asthma: executive summary. Bethesda Md: National Asthma Education Program, Office of Prevention, Education, and Control; National Heart, Lung, and Blood Institute, 1991. National Institutes of Health publication No. 91-3042.
6. British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. Guidelines for the management of asthma in adults: I-chronic, persistent asthma. BMJ 1990; 301:651-3.
7. British Thoracic Society, Research Unit of the Royal College of Physicians of London, King's Fund Centre, National Asthma Campaign. Guidelines for the management of asthma in adults: II-acute severe asthma. BMJ 1990; 301:797-800.
8. Levison H. Canadian consensus on the treatment of asthma in children. Can Med Assoc J 1991; 145:1449-55.
9. 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.
10. Britton MG, Earnshaw JS, Palmer JBD. A twelve month comparison of salmeterol with salbutamol in asthmatic patients. Eur Respir J 1992; 5:1062-87.
11. D'Alonzo GE, Nathan RA, Henochowicz S, Morris RJ, Ratner P, Rennard SI. Salmeterol xinafoate as maintenance therapy compared with albuterol in patients with asthma. JAMA 1994; 271:1412-6.
12. Nathan RA, Seltzer JM, Kemp JP, Chervinsky P, Alexander WJ, Liddle R, Mills R. Safety of salmeterol in the maintenance treatment of asthma. Ann Allergy Asthma Immunol 1995; 75:243-8.
13. Bousquet J, Aubert B, Bons J. Comparison of salmeterol with disodium cromoglycate in the treatment of adult asthma. Ann Allergy Asthma Immunol 1996; 76:189-94.
14. Fitzpatrick MF, Mackay T, Driver H, Douglas NJ. Salmeterol in nocturnal asthma: a double-blind, placebo-controlled trial of a long-acting inhaled β_2-agonist. BMJ 1990;301:1365-8.
15. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987; 136:225-44.
16. Gardner RM. Standardization of spirometry: a summary of recommendations from the American Thoracic Society. The 1987 update. Ann Intern Med 1988; 108:217-20.
17. van Elteren PH. On the combination of independent two-sample tests of Wilcoxon. Bull Int Stat Inst 1958; 37(Pt 3):351-61.
18. Lundbäck B. A 3 months comparison of salmeterol and albuterol dry powder in mild to moderate asthmatic patients [abstract]. Am Rev Respir Dis 1991; 143:A651.
19. Fjellbirkeland L, Gulsvik A, Palmer JBD. The efficacy and tolerability of inhaled salmeterol and individually dose-titrated, sustained-release theophylline in patients with reversible airways disease. Respir Med 1994; 88:599-607.
20. Brambilla C, Chastang C, Georges D, Bertin L. Salmeterol compared with slow-release terbutaline in nocturnal asthma. Allergy 1994; 49:421-6.
21. Greening AP, Ind PW, Northfield M, Shaw G, on behalf of Allen & Hanburys Limited UK Study Group. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. Lancet 1994; 344:219-24.
22. Lundbäck B, Rawlinson DW, Palmer JB. Twelve month comparison of salmeterol and salbutamol as dry powder formulations in asthmatic patients. Thorax 1993; 48:148-53.
23. Charpin D, Vervloet D, Bons J, and a French Multicentre Study Group. Quality of life in moderate chronic asthma: salmeterol versus current treatments [abstract]. J Allergy Clin Immunol 1992; 89(1 Pt 2):189.
24. Highlights of the expert panel report 2: Guidelines for the diagnosis and management of asthma. Bethesda, Md: National Institutes of Health, National Heart, Lung, and Blood Institute, 1997. NIH publication No. 97-4051A.