

Effects of β_2 -agonists on airway tone and bronchial responsiveness

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In evaluating the clinical consequences of β_2 -agonist therapy, it is important to consider the possibility of reduced asthma control and increased bronchial responsiveness with regular or long-term use. Some studies have noted reductions in protective effects but not complete loss of protection with short-acting β_2 -agonist therapy. These reductions vary, depending on the use of nonspecific, indirect, or immunologic challenges, but it appears there is a greater loss of protective effect against indirect stimuli. Tachyphylaxis to the bronchodilatory effects of long-acting β_2 -agonists appears to be minimal. Individuals homozygous for arginine at locus 16 of the β_2 -adrenergic receptor gene have a decline in pulmonary function during β_2 -agonist use, and they are at greater risk of asthma exacerbations during β_2 -agonist therapy than patients with other genotypes. Important questions for further research are whether small differences in tachyphylaxis and bronchoprotection have relevant clinical effects and to what extent tachyphylaxis and tolerance to bronchoprotection are caused by pharmacogenetic interactions. (*J Allergy Clin Immunol* 2002;110:S304-12.)

Key words: Asthma, β_2 -agonist, combination therapy, corticosteroid, pharmacogenetics, tachyphylaxis

β_2 -Adrenergic receptor (β_2 AR) agonists are effective bronchodilators that are widely used for the treatment of asthma. Inhaled formulations are preferred because of their convenience and ease of use.¹

Current guidelines recommend using short-acting β_2 -agonists (SABAs) on an as-needed basis for symptom control as opposed to inhaling as a scheduled medication.² Tachyphylaxis with reduced bronchodilation over time with regular β_2 -agonists is a potentially important finding that appears to occur more often with SABAs. The bronchoprotective effects of β_2 -agonists against direct and indirect stimulants vary considerably and are characterized by some degree of tachyphylaxis. Interaction between inflammatory cells and mediators and the effects on mucous secretion and clearance may influence bronchodilatory responses with β_2 -agonists. These pharmacologic interactions with inflammatory cells and mediator release are better understood in vitro than in vivo.

It is currently recommended that long-acting β -agonists (LABAs) be combined with an inhaled corticoste-

Abbreviations used

EIB: Exercise-induced bronchospasm
ICS: Inhaled corticosteroid
LABA: Long-acting β_2 -agonist
PC20: Provocation concentrations causing a decrease in FEV₁ of 20%
PEF: Peak expiratory flow
SABA: Short-acting β_2 -agonist

roid (ICS), since this combination produces improved asthma control and permits the use of lower doses of ICS.^{3,4} In a study by Greening et al,³ adult asthmatic patients who were symptomatic despite maintenance ICS were randomly assigned to have the addition of either high-dose ICS or salmeterol. The ICS/salmeterol group had a larger increase in morning peak expiratory flow (PEF) compared with the higher-dose ICS group as well as significant improvements in diurnal variation in PEF and use of a rescue bronchodilator (salbutamol, an alternate name for albuterol). Woolcock et al⁴ performed a similar study, adding either high-dose ICS or salmeterol to maintenance ICS. Again, larger improvements in morning PEF and in the percentage of symptom-free and rescue-free days were noted in the ICS/salmeterol group in comparison with the higher-dose ICS group.

This article reviews the effects of SABAs and LABAs on airway tone and bronchial responsiveness and the effect of β_2 AR genotype on pulmonary function.

EVALUATING BRONCHODILATOR RESPONSES TO β_2 -AGONIST THERAPY

Short-acting β_2 -agonists

Inhaled β_2 -agonists directly relax airway smooth muscle and are useful for short-term relief or prevention of asthma symptoms.¹ Albuterol is a selective SABA that provides rapid bronchodilation lasting 4 to 6 hours. Recently, Drazen et al² showed no detrimental effect of regular SABA use in subjects with mild to moderately severe asthma. However, there was no clinical benefit to using albuterol on a regular schedule rather than as needed. In this study, subjects who inhaled albuterol on a regular schedule used 5 times more than those who administered it as needed, but there was no evidence of tachyphylaxis. More importantly, there was no significant difference in asthma control between the treatment groups.

In a study evaluating the short-term response to β_2 -agonists, improvement in FEV₁ was maintained over a

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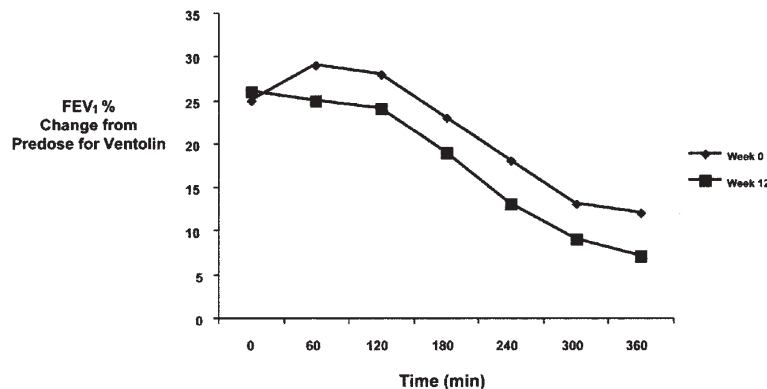


FIG 1. Changes in FEV₁ with albuterol formulated with hydrofluoroalkane. Ventolin is albuterol formulated with chlorofluorocarbon. (From Bleecker ER, Tinkelman DG, Ramsdell J, et al. Proventil HFA provides bronchodilation comparable to ventolin over 12 weeks of regular use in asthmatics. *Chest* 1998;113:283-9. With permission.)

12-week period, although there was a small degree of tachyphylaxis with regular use (Fig 1). Two groups of patients with asthma were treated with albuterol inhalers containing hydrofluoroalkane or chlorofluorocarbon as the propellant.⁵ There was an approximate 20% reduction in the bronchodilator response beginning at week 4, which persisted unchanged during the next 8 weeks of this study. The peak FEV₁ effect, duration of FEV₁ effect, and area under the curve for FEV₁ were all smaller at weeks 4, 8, and 12 than at week 0 for both the hydrofluoroalkane albuterol and chlorofluorocarbon albuterol groups. The fact that peak effect and duration of effect were the same in both groups is a good demonstration of the intrinsic characteristics of albuterol used on a regular basis. The small loss of bronchodilator response may have little clinical significance because overall bronchodilation was maintained and did not decrease further as the trial progressed. A companion study further illustrates the safety of this class of short-acting β_2 -agonists by using this SABA continuously.⁶ Regular use of albuterol formulated in either hydrofluoroalkane or chlorofluorocarbon did not cause asthma control to deteriorate, as measured by adverse event reporting rates and asthma symptom scores.

Use of SABAs over longer periods has been evaluated alone and in combination with ICS. Van Essen-Zandvliet et al⁷ randomly assigned 116 children with asthma to treatment with an inhaled β_2 -agonist (0.2 mg salbutamol) plus an ICS (0.2 mg budesonide) 3 times per day or to an inhaled β_2 -agonist plus a placebo 3 times per day. Of note, 26 patients receiving β_2 -agonist plus placebo withdrew from the study, mainly because of worsening asthma symptoms, compared with 3 withdrawals in the group receiving β_2 -agonist and ICS. There was an absolute increase in prebronchodilator FEV₁ of 7% after 2 months of β_2 -agonist plus ICS compared with a decrease of 4% after 2 months of β_2 -agonist and placebo. This 11% difference indicated FEV₁ was maintained during the median 22-month follow-up period. An absolute increase of 3.7% was observed with postbronchodilator FEV₁ within 2 months in patients receiving β_2 -agonist plus ICS,

and an absolute decrease of 1.1% was observed in children receiving β_2 -agonist plus placebo. The difference between the two treatment groups was maintained. In the β_2 -agonist plus ICS group, the average rate of PEF increased from baseline by 36.6 L/min compared with 3.7 L/min in the β_2 -agonist plus placebo group. This difference was maintained throughout the follow-up period.

Long-acting β_2 -agonists

The short duration of action of albuterol and the need for improved β_2 -agonist controller agents led to the development of LABAs. Salmeterol is a highly selective, potent LABA indicated for the long-term maintenance treatment of asthma and prevention of bronchospasm in patients with reversible obstructive airway disease. Salmeterol has a lipophilic chain that allows prolonged binding to the β_2 AR. Initial studies testing the efficacy of salmeterol compared with albuterol noted the duration of effect of albuterol to be approximately 3.5 hours, whereas salmeterol maintained its effect for nearly 12 hours.⁸ The area under the curve for salmeterol therapy was larger than that measured for two successive doses of albuterol administered at 6-hour intervals. During the 12-week study period, the effects of salmeterol on FEV₁ were maintained. Over time, there was a small decline in the bronchodilation from albuterol, comparable with the level of the tachyphylaxis noted in other reports. An improvement in baseline airway caliber was noted in the salmeterol group, suggesting little or no tachyphylaxis after therapy for 3 months with salmeterol.

A study by Lundback et al⁹ evaluated the improvement in lung function as measured by change in FEV₁ over a 12-month period with salmeterol therapy. Treatment resulted in an increase in FEV₁ throughout the study period. Other findings were that 50 μ g salmeterol twice daily was more effective than 400 μ g salbutamol 4 times daily in the control of asthma over a period of 3 months and was more effective than 400 μ g salbutamol twice daily over a further 9-month period. Neither salmeterol nor salbutamol was associated with worsening of asthma control as measured by number and frequency of exacerbations.

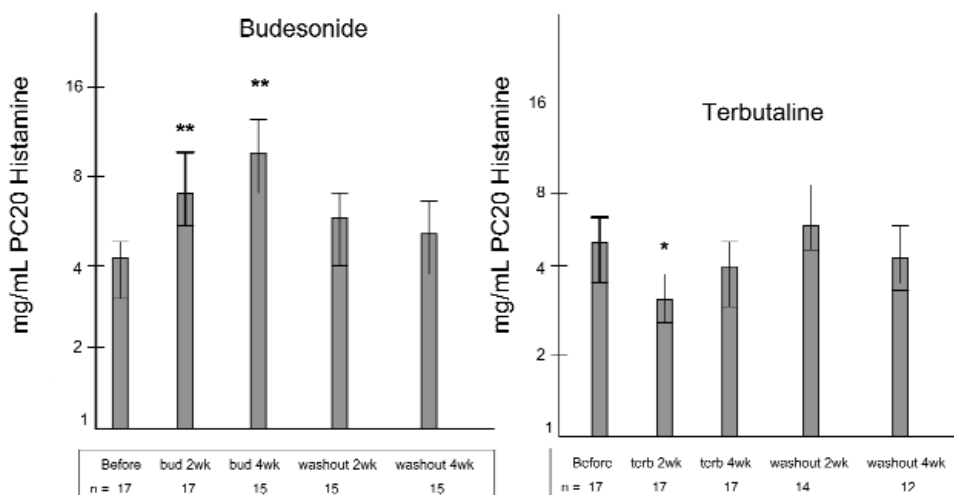


FIG 2. Effect of treatment with budesonide and terbutaline on bronchial responsiveness. (From Kraan J, Koëter GH, vd Mark TW, et al. Changes in bronchial hyperreactivity induced by 4 weeks of treatment with antiasthmatic drugs in patients with allergic asthma: a comparison between budesonide and terbutaline. *J Allergy Clin Immunol* 1985;76:628-36. With permission.)

Response to albuterol after LABA therapy

Nelson et al¹⁰ conducted two placebo-controlled crossover studies to assess bronchodilator response to a SABA before and after long-term therapy with salmeterol. Patients in one study were corticosteroid-naïve; patients in the other study were treated with an ICS. After a 2-week β_2 -agonist washout period, before administering the study medication on day 1 and again after 28 days of therapy, changes in FEV₁ after cumulative doubling doses of inhaled albuterol were determined. There were significant increases from predose FEV₁ values, from the lowest dose of albuterol throughout the dose-response assessment ($P \leq .001$) on both assessment days for salmeterol and during placebo administration periods. Increases in FEV₁ were maintained for 6 hours after the last dose of albuterol ($P < .05$). There were no statistically significant differences in the albuterol dose response after salmeterol or placebo. These studies show that continual therapy with salmeterol does not result in tolerance to the acute bronchodilator effects of albuterol, with concomitant ICS treatment.

Another LABA, formoterol, differs from salmeterol because it is a full β_2 -agonist and thus similar to isoproterenol. Formoterol, because of hydrophilic responses, has a more rapid onset of action than does salmeterol. Formoterol is similar to salmeterol with respect to duration of bronchodilator response over a 12-hour period and additive effects with ICS.¹¹⁻¹³

PROTECTIVE EFFECTS OF β_2 -AGONISTS ON BRONCHIAL RESPONSIVENESS

It has been shown that regular inhalation of SABAs by asthmatic patients with allergies may lead to a slight and transient increase in bronchial responsiveness, measured as a greater degree of bronchial hyperresponsiveness after cessation of treatment when compared with base-

line pretreatment levels. This effect has been observed in some but not all studies of a variety of SABAs such as albuterol, terbutaline, and fenoterol.¹⁴⁻¹⁶ When it occurs, bronchial hyperresponsiveness may persist for a number of days after cessation of therapy.

A small increase in bronchial responsiveness was noted by Kraan et al,¹⁷ who performed a double-blinded, crossover study comparing the effects of long-term treatment with inhaled budesonide and terbutaline on bronchial responsiveness in 17 patients with allergic asthma. Both drugs were administered for 4 weeks with a placebo treatment period before and after each active treatment period. To assess bronchial responsiveness, provocation tests with histamine and propranolol were performed every 2 weeks. Before each challenge, terbutaline and budesonide were withheld for at least 12 hours. Before the budesonide treatment, the FEV₁ value (percent predicted) was 85.3%. After 2 and 4 weeks of treatment with this drug, the value increased significantly to 89.4% and 96.2%, respectively. The histamine provocation concentrations causing a decrease in FEV₁ of 20% (PC₂₀) were 4.0, 7.2, and 9.5 mg/mL, respectively, on these study days. The PC₂₀ values for propranolol, which were measured 1 hour after the histamine provocation, were 11.7, 13.3, and 14.0 mg/mL. The FEV₁ values before and after 2 and 4 weeks of treatment with terbutaline were between 85% and 87%. The histamine PC₂₀ values on the same days were between 3.1 and 4.7 mg/mL. The propranolol PC₂₀ values were 14.2, 8.7, and 10.1 mg/mL. Thus, budesonide improved bronchial responsiveness, whereas treatment with terbutaline led to a temporary and very small increase of bronchial hyperreactivity, possibly as a result of β_2 AR desensitization. These slight changes in bronchial responsiveness are close to if not at the limit of accurate measurement and may not be clinically significant in terms of overall asthma control (Fig 2).

PROTECTIVE EFFECTS OF β_2 -AGONISTS TO ALLERGEN

Bronchoprotection against provoking stimuli has been shown to diminish with regular use of SABAs, and bronchial responsiveness to allergen may be increased. In one study, after 1 week of albuterol therapy (200 μ g 4 times daily), the late asthmatic response was increased (23.1% FEV₁ decline vs 13.2% at baseline) and allergen-induced airway responsiveness was slightly increased (change in log methacholine PC20 0.37 vs 0.20 μ g/mL at baseline). This suggests that the combination of regular use of inhaled β_2 -agonists and allergen exposure may increase bronchial inflammation, resulting in more severe delayed responses caused by increased mediator release from mast cells or other effector cells.¹⁸

PROTECTIVE EFFECTS OF β_2 -AGONISTS AGAINST BRONCHOCONSTRICTION

Although there is minimal tachyphylaxis to the bronchodilator effects of β_2 -agonists, several studies have demonstrated marked levels of tolerance to their non-bronchodilatory effects, namely the protective effects of β_2 -agonists against bronchoconstriction caused by histamine,¹⁴ methacholine,¹⁹ or adenosine monophosphate. O'Connor et al²⁰ found that after regular use of terbutaline, the protective effect against adenosine monophosphate was more diminished than the protective effect against methacholine (a direct bronchoconstrictor). Cockcroft et al²¹ reported similar findings, showing that after regular use of salbutamol for 2 weeks, airway responsiveness to allergens (bronchoconstriction induced by mast cell mediator release) had increased, whereas responsiveness to methacholine had not changed (Fig 3). Furthermore, they found that regular use of salbutamol caused tolerance to the protective effect of salbutamol on bronchoconstriction induced by both methacholine and allergens. These findings support the possibility of β_2 AR down-regulation on airway smooth muscle and probably to an even greater extent on mast cells or other inflammatory cells. The latter may result in an enhanced effect on the late asthmatic response, which is probably a more important consequence of the level of allergen exposure, since administration of a β_2 -agonist may protect against the acute response after allergen exposure, allowing a larger allergen exposure and a more severe delayed response.¹⁸

EFFECTS OF β_2 -AGONISTS ON EXERCISE-INDUCED BRONCHOSPASM

Salmeterol has been shown to have a prolonged effect against exercise-induced bronchospasm (EIB), which occurs in most patients with clinically diagnosed asthma. EIB is thought to be produced by hyperventilation during exercise that causes airway cooling and possibly inflammatory mediator release.²² Therapy with β_2 -agonists is the primary treatment of this condition. When used before exer-

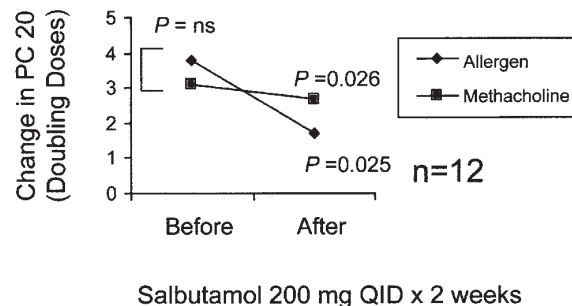


FIG 3. Tolerance to the bronchoprotective effects of inhaled salbutamol. (Data from Cockcroft DW, McParland CP, Britto SA, et al. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993;342:833-7.)

cise, SABAs such as albuterol prevent EIB in most patients with asthma, but the protection lasts less than 3 hours.

Kemp et al²³ assessed whether a single dose of inhaled salmeterol (42 μ g) was effective prophylaxis against EIB and whether it could attenuate bronchoconstriction in subjects undergoing repeated exercise challenges over a period of 12 hours. In total, 161 patients were randomly assigned to receive either 180 μ g salmeterol or 180 μ g albuterol in two similar studies. Three exercise challenges were conducted over a 12-hour period and consisted of 5 to 10 minutes of treadmill exercise while subjects inhaled dry air (0% humidity) at ambient temperature. Airway function after the serial challenges was assessed as change in FEV₁ compared with predose values. The mean maximal percentage decrease in FEV₁ after the three exercise challenges was 5% at 0.5 hour, 8% at 5.5 hours, and 13% at 11.5 hours after β_2 -agonist administration in the salmeterol group compared with 7%, 25%, and 27%, respectively, in the albuterol group and 27%, 27%, and 26%, respectively, in the placebo group ($P < .001$). Albuterol provided complete protection against EIB (defined as <10% decrease in FEV₁ compared with predose values) only after the first exercise challenge, but salmeterol continued to provide complete protection in the majority of subjects after each exercise challenge: 80% at 0.5 hour, 70% at 5.5 hours, and 55% at 11.5 hours. These data demonstrate that salmeterol prevents or reduces the response to exercise for up to 12 hours²³ (Fig 4).

Nelson et al²⁴ performed a random-order, double-blinded, crossover trial of 20 patients with exercise-induced asthma. Each patient received inhaled salmeterol or placebo twice daily for 1 month, with a 1-week washout period between treatments. The patients performed cycle ergometry while breathing cold, dry air (0% humidity) 30 minutes after the morning dose and 9 hours later on the 1st, 14th, and 29th study days. The primary end point was the extent of the decrease in FEV₁ 10 minutes after exercise. With placebo, significant airway narrowing developed at all times (mean decrease from baseline FEV₁, 19% in the morning and 18% in the evening). The morning dose of salmeterol attenuated the degree of bronchoconstriction at all times (decrease in FEV₁ on day 1, 5%; on day 14, 10%; and on day 29, 9%). The ability

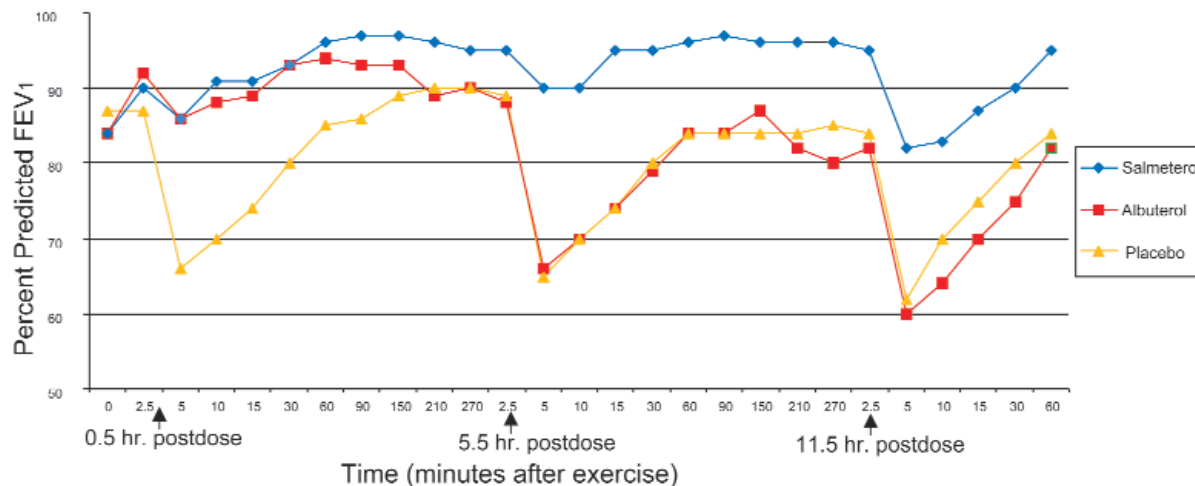


FIG 4. Prolonged effect of salmeterol against EIB. (From Kemp JP, Dockhorn RJ, Busse WW, et al. Prolonged effect of inhaled salmeterol against exercise-induced bronchospasm. *Am J Respir Crit Care Med* 1994;150:1612-5. With permission.)

of salmeterol to act throughout the day decreased with long-term administration (decrease in FEV₁ from morning to evening on day 1, 6%; on day 14, 15%; and on day 29, 14%). Thus, protection against exercise-induced asthma was maintained with long-term administration of salmeterol, but the length of time that the drug remained protective after a single dose decreased.

BRONCHOPROTECTIVE EFFECTS OF LABAs

Further studies have been performed to evaluate whether clinically important tachyphylaxis develops to the bronchoprotection afforded by the LABAs. Some of the studies reporting tachyphylaxis used provocations that patients either would not encounter in their daily lives, for example, histamine, methacholine, and adenosine, or for which β_2 -agonists would not be given as primary therapy, for example, antigen. With long-term administration of salmeterol, the extent of protection against experimental precipitants of asthma such as methacholine and adenosine may decrease.

Regular use of salmeterol has been associated with a reduced protective effect against methacholine-induced bronchoconstriction at 4 and 8 weeks.¹⁹ The study by Bhagat et al²⁵ was designed to determine if regularly inhaled salmeterol for a short period leads to tolerance to its bronchoprotective effect against methacholine. Ten asthmatic volunteers who withheld β_2 -agonist therapy for 4 weeks before and during the study participated in a double-blinded, crossover study with two random-order treatment periods: inhaled salmeterol (50 μ g) twice daily for 7 doses and placebo in similar fashion. Methacholine inhalation challenges were performed 1 hour after doses 1, 3, 5, and 7, and then 24 hours after the last dose of the study inhaler, 10 minutes after 200 μ g of salbutamol. The baseline FEV₁ value before doses 3, 5, and 7 of salme-

terol, that is, 12 hours after salmeterol, was significantly higher than all other values. Twenty-four hours after the last dose of salmeterol, the FEV₁ value was no different from that during the placebo period. The PC20 to methacholine after the first dose of salmeterol (6.1 mg/mL) was statistically similar to the value achieved 10 minutes after salbutamol, after the placebo period (8.3 mg/mL), and these were larger than the second, third, and fourth salmeterol days (3.4, 2.6, and 1.9 mg/mL, respectively). Tolerance to the acute bronchoprotective effect of salmeterol occurred after the first 2 doses and progressively increased to the 7th dose. Tolerance to the acute bronchoprotective effect of salbutamol was significant after regular use of salmeterol for 7 doses.

This study showed reduced bronchoprotective effects of salmeterol against methacholine challenge independent of the use of ICS. However, it was conducted during a short period. A 24-week trial was performed to determine whether a progressive reduction in bronchoprotection occurs and leads to clinical instability of asthma.²⁶ A total of 408 patients were randomly assigned to twice-daily salmeterol (42 μ g) or placebo and had methacholine challenges performed 10 to 14 hours after dosing during treatment weeks 4, 12, and 24, as well as 3 and 7 days after treatment. Over 24 weeks of treatment, salmeterol provided significant protection against methacholine-induced bronchoconstriction of approximately one doubling dose of methacholine when compared with placebo, with no evidence of a progressive decrease in protection. A rebound increase in airway hyperresponsiveness was not observed 3 or 7 days after cessation of salmeterol therapy (Fig 5). These results are similar to previous results showing protection against methacholine-induced bronchoconstriction of 0.6 to 1.2 doubling doses approximately 12 hours after dosing during an 8-week treatment period.²⁷

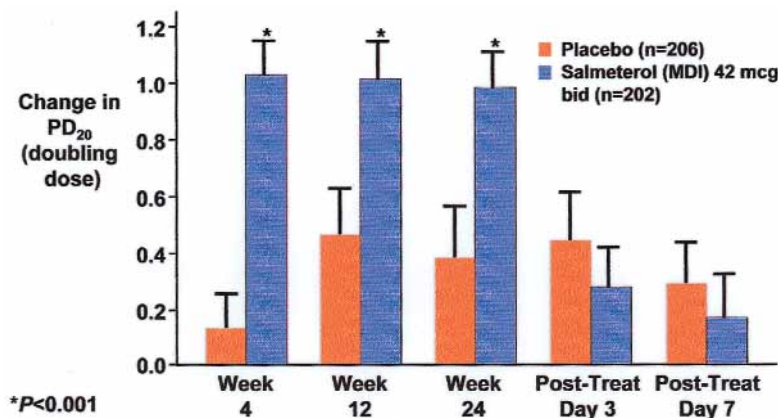


FIG 5. Change in airway hyperresponsiveness over 24 weeks. MDI, Metered-dose inhaler. (Data from Rosenthal RR, Busse WW, Kemp JP, et al. Effect of long-term salmeterol therapy compared with as-needed albuterol use on airway hyperresponsiveness. *Chest* 1999;116:595-602.)

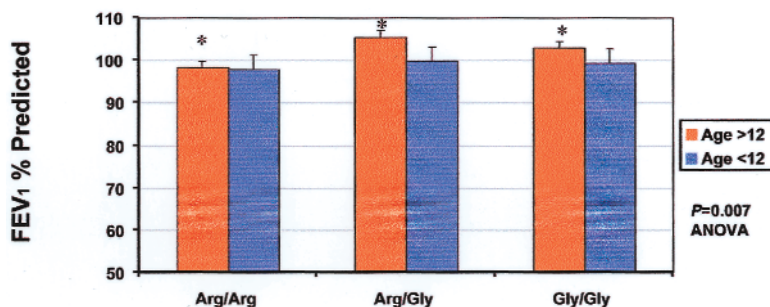


FIG 6. Effect of β_2 AR genotype on baseline pulmonary function. ANOVA, Analysis of variance. (Data from Summerhill E, Leavitt SA, Gidley H, et al. β_2 -Adrenergic receptor Arg16/Arg16 genotype is associated with reduced lung function, but not with asthma, in the Hutterites. *Am J Respir Crit Care Med* 2000;162:599-602.)

Some studies suggest that regular use of β_2 -agonists might result in tolerance to their protective effects against bronchoconstrictive stimuli even if their bronchodilatory properties remain unchanged.¹⁵ In a direct comparison, Cloosterman et al²⁸ evaluated whether tachyphylaxis occurs during the use of SABAs or LABAs by allergic patients with asthma. The patients were randomly assigned to monotherapy with 200 μ g salbutamol QID, 12 μ g formoterol BID, or placebo after an 8-week washout period, for 12 weeks of total therapy. At the start of the treatment period and every 4 weeks thereafter, spirometry and bronchial challenge with histamine PC20 were performed. Both FEV₁ (−6.6%) and bronchial responsiveness (−1.2 doubling concentration) decreased during regular salbutamol use. There were no significant changes in FEV₁ and PC20 observed in either the formoterol group or the placebo group. These results showed that regular use of the SABA salbutamol in asthmatic patients with allergies may result in a deterioration of bronchial responsiveness, as measured by histamine PC20, and in a small decline in FEV₁, which was not the case during regular use of the LABA formoterol.

EFFECT OF β_2 AR GENOTYPE ON PULMONARY FUNCTION

The β_2 AR gene is located on chromosome 5q23-31 in a region that has been linked with asthma, bronchial hyperresponsiveness, and allergic phenotypes.²⁹⁻³³ Liggett³⁴ sequenced the β_2 AR gene and reported several polymorphisms. The most frequent and important appear to be those at loci 16 and 27. Sequence variants at these loci can affect receptor down-regulation and may be associated with nocturnal asthma.³⁵ Summerhill et al³⁶ genotyped polymorphisms at positions 16 and 27. The Arg16Gly and Gln27Glu polymorphisms showed no evidence of linkage to qualitative measures of asthma and bronchial hyperresponsiveness. However, FEV₁ percent predicted and FVC percent predicted were significantly lower among adults and adolescents homozygous for arginine at locus 16. Similar reductions were observed for subjects >12 years of age who were heterozygous at locus 16 but not for heterozygotes at ≤ 12 years of age. Thus, changes in this gene may be related to decline in pulmonary function over time in adults (Fig 6).

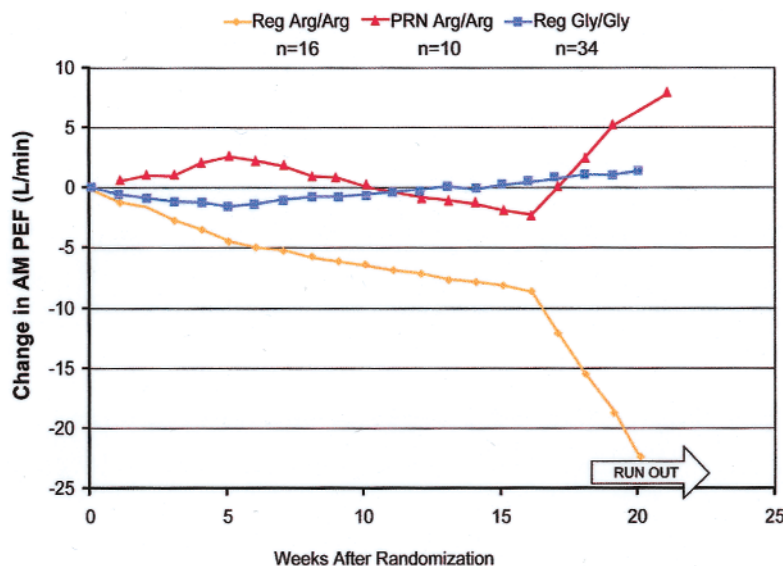


FIG 7. Comparison of response to albuterol QID or PRN by genotype. (From Israel E, Drazen JM, Liggett SB, et al. The effect of polymorphisms of the β_2 -adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med* 2000;162:75-80. With permission.)

There has been significant interest in the effects of β_2 AR polymorphisms in response to therapy with SABAs and LABAs. Using a large cohort of 190 well-characterized patients with mild asthma, Israel et al³⁷ demonstrated that regular use of β_2 -agonists can produce different bronchodilator responses that appear to be related to specific polymorphisms in the β_2 AR gene. In this retrospective study, the subjects were analyzed for polymorphisms at locus 16, and the effects of regular versus as-needed albuterol use were compared. Regular β_2 -agonist use was associated with reductions in both morning and evening PEF in patients with Arg16Arg. In addition, individuals with Arg16Arg receiving regular β_2 -agonist therapy showed a further decrease in morning PEF after the SABA was discontinued at a time interval when other studies have reported increases in bronchial responsiveness with β_2 -agonist therapy. This deterioration in pulmonary function associated with regular use was specific to patients with Arg16Arg; Gly16Gly individuals did not have this effect. Furthermore, individuals with Arg16Arg who were treated with as-needed albuterol did not show these reductions in morning or evening peak flow. Polymorphisms at locus 27 of the β_2 AR did not alter the response to regular β_2 -agonist use in these asthmatic patients³⁷ (Fig 7). These data suggest that a proportion of patients (approximately 16% of patients have Arg16Arg) may not respond in the same manner as the general population, having a decline in airway function during regular β_2 -agonist use and a further decrease in pulmonary function when they discontinue high-dose β_2 -agonist therapy. Since a majority of patients with asthma use β_2 -agonists as primary therapy, potentially adverse pharmacogenetic interactions may have widespread clinical significance.

Taylor et al³⁸ retrospectively examined asthma control during long-term treatment with salbutamol and salme-

terol by stratifying the study results in relation to the three possible genotypes at locus 16. The principal finding was that among patients with Arg16Arg, the frequency of major exacerbations more than doubled during long-term treatment with salbutamol compared with placebo, whereas no specific adverse events occurred in patients with the other genotypes. The rate of major exacerbations during treatment with salbutamol was 5 times greater for patients with Arg16Arg than for patients with Gly16Gly. Compared with salbutamol, the outcomes for salmeterol were largely unaffected by the locus 16 genotype. Although the benefits of salmeterol appeared to be least in the Arg16Arg subgroup, in whom the rate of major exacerbations across genotypes was nearly 3 times that of Gly16Gly subjects, there was a similar pattern in the frequency of major exacerbations across genotypes during the placebo treatment period³⁸ (Fig 8).

Replication studies evaluating pharmacogenetic effects, such as the BARGE (Beta-Adrenergic Response by Genotype) trial currently being performed by the Asthma Clinical Research Network, are important. Avoidance of regular SABA therapy and careful monitoring may be indicated in patients with Arg16Arg. In addition, pharmacogenetic relations may partially explain the variation among individuals in onset and duration of bronchodilation and changes in bronchoprotection over time.

CONCLUSIONS

Multiple mechanisms may modulate clinical responses to β_2 -agonists. Genetic variation, receptor function, downstream signaling events, coexistent bronchial inflammation, pharmacologic properties of β -agonists (eg, potency, duration of action), and interactions with other drugs may affect overall response to therapy.

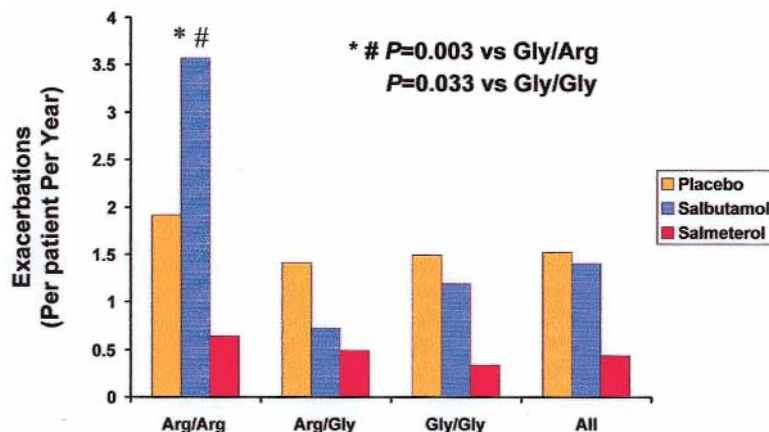


FIG 8. Influence of β_2 AR polymorphisms on asthma exacerbations. (From Taylor DR, Drazen JM, Herbison GP, et al. Asthma exacerbations during long-term β agonist use: influence of β_2 adrenoreceptor polymorphism. *Thorax* 2000;55:762-7. With permission.)

It is important to consider differences in study design when evaluating individual variation in therapeutic responses. Often, the activity and severity of airway disease are difficult to compare between studies. In addition, expression of results as mean group data may obscure individual differences.

Important questions for further research are whether small differences in tachyphylaxis and bronchoprotection have relevant clinical effects and to what extent tachyphylaxis and tolerance to bronchoprotection are caused by pharmacogenetic interactions.

DISCUSSION SESSION

Question: One of the intriguing observations that is being made by a number of groups is that regarding bronchoprotective tolerance with β -agonists, you cannot influence that tolerance with a corticosteroid. In the in vivo situation, are we seeing receptor sensitization or something with regard to the bronchodilation challenge methodology?

Dr Bleecker: A number of the studies I discussed were performed with patients using inhaled corticosteroids. In several of the studies, patients receiving β -agonists were not taking steroids. The slight loss of bronchoprotection seen was not changed by the presence of corticosteroid therapy.

Comment: In airway smooth muscle, steroids do not reverse β -desensitization. If you culture airway smooth muscle cells, expose them to a β -agonist over a short or long term, wash out the drug, and then give more of the agent, you see desensitization. If you pretreat the cells with dexamethasone for 2 hours or 24 hours, this has no effect on the ability to desensitize. Perhaps steroids reverse the β -desensitization in vivo. If so, this has nothing to do with what is going on in the smooth muscle.

Comment: There may be different cell specificities in whether the steroid is able to change the β -receptor desensitization. Exposing patients to high doses of salbutamol revealed a progressive loss of bronchodilatory activity. When these studies were repeated in the presence of a milligram of fluticasone, the decline in lung function response did not occur. One would presume that this reflects a smooth muscle response. However, this may be an integrated system that is picking up other activities. It is intriguing that inhaled or oral steroids do not appear to offset the loss of bronchoprotec-

tion seen with chronic β -agonist treatment. There does not appear to be a difference between short- and long-acting β -agonists. Full agonists tend to produce this effect more than the partial agonists. **Comment:** We may be oversimplifying this. There is a great potential for cross-talk between one G-protein-coupled receptor and another. Many of the bronchoconstrictive signals that are present are in fact through GPCRs. So I wonder whether this effect may be due not to a loss of β -receptor function but an enhancement of some bronchoconstrictive elements.

Comment: The whole issue of tolerance is ridden with paradoxes. We have observed bronchodilator tolerance with short- and long-acting agents. The effect is best measured in patients during bronchoconstriction. It is difficult to measure bronchodilator tolerance in stable patients. If tolerance matters, it is really difficult to define when or under what circumstances. There are no clinical studies that relate the variability in tolerance between patients receiving short- and long-term treatment.

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