

Long-acting β -agonists and exercise

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Since the first reported use of “adrenal substance” for acute asthma in 1900,¹ adrenergic receptor agonists have long been the agents of choice for relieving acute symptoms of asthma. Considerable pharmacologic research has subsequently gone into the development of variations of these receptor agonists, resulting in agents with more specific targeting of the β_2 -adrenergic receptor and much longer duration of action. Salmeterol and formoterol are the currently available longest-acting β_2 -agonists, commonly abbreviated as LABAs, although even longer-acting ones have been developed for anticipated marketing.² The primary established role for a LABA is as additive maintenance therapy to inhaled corticosteroids.^{3,4} It is as daily maintenance therapy that LABAs have generated controversy and led to the current “black-box” warning associated with salmeterol and formoterol.^{5,6}

In addition to providing acute bronchodilatation to relieve acute symptoms of asthma, inhaled β_2 -adrenergic receptor agonists have been used as highly effective prophylaxis for exercise-induced asthma. Like their shorter-acting predecessors, LABAs also have bronchoprotective effects for exercise-induced bronchospasm. The purpose of this editorial is to examine their role with regard to exercise.

EXERCISE AND DYSPNEA

Exercise-induced asthma has been the most commonly recognized cause of exercise-induced dyspnea in otherwise healthy children and adolescents. Asthma produces dyspnea during exercise because of airway obstruction from bronchospasm, and that airway obstruction can be prevented by the bronchoprotective effect of inhaled β_2 -adrenergic agonists. When that bronchoprotective effect is not apparent in preventing exercise-induced dyspnea, that might either represent bronchospasm caused by development of tolerance to the bronchoprotective effect of the β_2 -agonist or a cause of exercise-induced dyspnea other than asthma.⁷ Because inhaled β_2 -adrenergic agonists, such as albuterol and terbutaline, have been so effective at preventing exercise-induced dyspnea when it is caused by bronchospasm, there is the expectation that the longer-acting inhaled β_2 -adrenergic agonists will provide more sustained bronchoprotective effect.

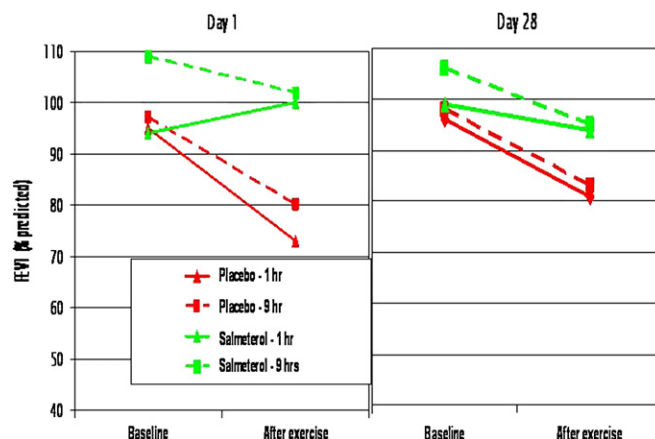


FIG 1. Mean percent predicted FEV₁ at baseline before and after exercise on days 1 and 28 of 50 μ g of salmeterol or placebo administered each morning in sixteen 12- to 16-year-old subjects also receiving twice-daily inhaled corticosteroids. This was a randomized, double-blind crossover study.¹⁰

LABAS AND EXERCISE-INDUCED ASTHMA

Initial doses of both salmeterol and formoterol have similar but more sustained bronchoprotective effects for exercise-induced bronchospasm than shorter-acting bronchodilators, such as albuterol.⁸ However, an examination of 20 adults given salmeterol twice daily for 4 weeks showed that although a bronchodilator effect was maintained, a decrease in bronchoprotective effect for exercise-induced bronchospasm at 14 and 29 days of administration that was most prominent 9 hours after the dose was demonstrated.⁹

This loss of bronchoprotective effect has also been reported to occur even with use of inhaled corticosteroids. In a study of sixteen 12- to 16-year-old children receiving an inhaled corticosteroid, Simons et al¹⁰ showed an initial protective effect of a 50- μ g morning dose of salmeterol against exercise-induced asthma. Although the degree of protective effect in the morning 1 hour after the dose was greater than that at an afternoon exercise study 9 hours after the first morning dose, the protective effect was still significantly greater than that seen during placebo administration. After 28 days, although bronchodilatation persisted, the bronchoprotective effect was reported as having waned based on presenting the data as a maximum percentage decrease in FEV₁. However, although the magnitude of decrease in exercise-induced bronchospasm was not significantly different from that with placebo at 9 hours, the actual FEV₁ at 9 hours after salmeterol was still better than the 9-hour postexercise value after placebo (Fig 1).

These data suggest the loss of bronchoprotective effect to exercise is, on average, small and likely to be of little importance for most patients. However, Anderson and Brannon,¹¹ in a comprehensive review of β_2 -agonists and exercise-induced asthma, presented data indicating that, as a class, these agents are associated with considerable interpatient variability in the degree of decrease in duration for bronchoprotective effect and recovery of lung function in response to a β_2 -agonist. Although the factors

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TABLE I. Results of 4 exercise studies in 2 patients, ages 15 and 10 years, receiving inhaled corticosteroids, with and without concurrent administration of salmeterol

Patient no.	Day	Maintenance medication	Medication taken before exercise	FEV ₁ before exercise (L)	Decrease in FEV ₁ during exercise (%)	Exercise duration and symptoms
1*	1 d after admission	Budesonide (Pulmicort Turbuhaler), 200 µg twice daily, and salmeterol (Serevent MDI), 50 µg twice daily	Pirbuterol (Maxair Autohaler), 2 inhalations	2.83	42	Highest heart rate, 157 beats/min; target heart rate not attained because of dyspnea after 4 min
	5 d after admission	Budesonide, 200 µg twice daily, and salmeterol, 50 µg twice daily	Pirbuterol, 4 inhalations	3.26	55	Highest heart rate, 158 beats/min; target heart rate not attained because of dyspnea after 4 min
	9 d after admission	Budesonide, 200 µg twice daily, and SR theophylline, 225 mg twice daily (serum theophylline concentration, 15 µg/mL)	Pirbuterol, 4 inhalations	3.60	1	9 min, with highest heart rate of 173 beats/min and no dyspnea
	18 d after admission	Budesonide, 200 µg twice daily, and SR theophylline, 225 mg twice daily	Pirbuterol, 4 inhalations	3.56	1	10 min, with highest heart rate of 172 beats/min and no dyspnea
2†	Before admission	2 inhalations twice daily of fluticasone, 500 µg, in combination with salmeterol, 50 µg (Advair 500/50)	Albuterol, 4 inhalations from an MDI	1.43	71	3 min, with severe dyspnea and hypoxemia (oxygen saturation, 82%)
	Day of admission	1 inhalation twice daily of fluticasone 250 µg, in combination with salmeterol, 50 µg	Albuterol, 4 inhalations from an MDI	1.88	68	3 min with severe dyspnea and hypoxemia (oxygen saturation, 82%)
	2 d after admission	Budesonide, 200 µg twice daily, and SR theophylline, 250 mg twice daily (serum theophylline concentration, 9 µg/mL)	Albuterol, 4 inhalations from an MDI	1.98	51	9 min, with highest heart rate of 168 beats/min, no hypoxemia, and rapid spontaneous improvement
	3 d after admission	Budesonide, 200 µg twice daily, and SR theophylline, 300 mg twice daily (serum theophylline concentration, 16 µg/mL)	Albuterol, 4 inhalations from an MDI	1.93	14	11 min, with highest heart rate of 172 beats/min, no dyspnea, and no decrease in oxygen saturation

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MDI, Metered-dose inhaler; SR, sustained release.

*The predicted FEV₁ for patient 1 was 3.45 L.

†The predicted FEV₁ for Patient 2 was 1.69 L.

underlying this variability have not been defined, there has been both speculation and controversy regarding polymorphisms of the β_2 -adrenergic receptor and clinical effect of LABAs.¹² An editorial regarding studies concluding no relationship of asthma control to polymorphisms suggested there were limitations in the data because patients requiring frequent use of shorter-acting agents were excluded. The concern was expressed that, "...in patients with difficult-to-manage asthma, many of whom take β_2 agonists to excess, treatment might itself contribute adversely rather than beneficially to their clinical status."¹³

A report of 2 patients presents an extreme example of apparent adverse effects caused by a LABA.¹⁴ Two boys, ages 10 and 15 years, were studied as inpatients because of repeated life-threatening episodes of bronchospasm. They both demonstrated complete absence of bronchoprotective effect for exercise-induced bronchospasm caused by a β_2 -agonist while receiving twice-daily salmeterol. Within a few days after cessation of salmeterol use and substitution of an alternative second agent to

the same dose of inhaled corticosteroid, complete blocking of exercise-induced bronchoprovocation with the same β_2 -agonist could be demonstrated (Table I). The dramatic results in these 2 patients are consistent with Dr Anderson's recommendation: "If a person who takes β_2 agonist daily, including a LABA, experiences problems with exercise, then the physician should consider changing the treatment regimen to achieve better control of exercise-induced asthma."¹¹

LABAS AND EXERCISE IN ATHLETES WHO DO NOT HAVE ASTHMA

Concern regarding use of β_2 -agonists among competitive athletes has led to examination of the potential for an ergogenic effect of LABAs on exercise for those with and without asthma. The World Anti-Doping Agency has included β_2 -agonists in their published Prohibited List with a Therapeutic Use Exemption for formoterol, salbutamol (albuterol), salmeterol, and terbutaline

when administered by means of inhalation. The International Olympic Committee requires documented evidence of asthma or exercise-induced bronchoconstriction to allow administration of β_2 -agonists during the Olympic Games. The importance of bronchodilators for preventing exercise-induced bronchospasm and the high frequency of exercise-induced bronchospasm in competitive athletes led to concern that there could be ergogenic performance-enhancing properties for these medications. Several studies have examined this issue for both LABAs and the shorter-acting β_2 -agonists. A recent review examined the results of 19 such studies.¹⁵ Four of the studies reviewed examined the effects of salmeterol, and 2 used formoterol. Subjects were highly trained athletes in all of the studies. No effects were seen from either the shorter-acting β_2 -agonists or the LABAs on any ergogenic measurement, including maximal oxygen use, anaerobic threshold, strength performance, blood lactate value, rate of perceived exertion, and psychomotor performance. The conclusion from this and previous reports on the subject was that there was no basis for restricting the use of these agents in competitive athletics because of concern over a doping ergogenic effect.

CONCLUSIONS

LABAs have been demonstrated to be useful for many patients whose symptoms are not adequately controlled with conventional doses of inhaled corticosteroids alone, and the combination products have provided convenience. Although bronchodilation is generally maintained, bronchoprotection for exercise-induced bronchospasm will be reduced both for the LABAs and for the traditional shorter-acting β_2 -agonists used before exercise to prevent exercise-induced bronchospasm in patients receiving maintenance therapy with LABAs. Examination of the variability of the data from various studies suggests the decreased bronchoprotection might be sufficiently small for many patients as to be of minimal clinical importance, but there appears to be considerable individual variability with exceptional patients for whom the consequent loss of bronchoprotective effect for exercise-induced bronchospasm from regular use of the LABAs will be of major clinical importance. Until some predictive marker is found to identify those at risk, clinicians would be wise to add LABAs

selectively rather than using combinations as initial therapy so as to identify the occasional patient in whom the induced tolerance results in decreased clinical response to the β_2 -agonist inhaler that the patient uses for rescue and before exercise.

REFERENCES

1. Solis-Cohen S. The use of adrenal substance in the treatment of asthma. *JAMA* 1900;34:1164.
2. LaForce C, Alexander M, Deckelmann R, Fabbri LM, Aisanov Z, Cameron R, et al. Indacaterol provides sustained 24 h bronchodilation on once-daily dosing in asthma: a 7-day dose-ranging study. *Allergy* 2008;63:103-11.
3. Greening AP, Ind P, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid (Allen & Hanburys Limited UK Study Group). *Lancet* 1994;344:219-24.
4. Woolcock A, Lundback B, Ringdal N, Jacques LA. Comparison of addition of salmeterol to inhaled steroids with doubling of the dose of inhaled steroid. *Am J Respir Crit Care Med* 1996;153:1481-8.
5. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky Pm, SMART Study Group. The salmeterol multicenter asthma research trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129:15-26.
6. Aaronson DW. The "black box" warning and allergy drugs. *J Allergy Clin Immunol* 2006;117:40-4.
7. Abu-Hasan M, Tannous B, Weinberger M. Exercise-induced dyspnea in children and adolescents: if not asthma then what? *Ann Allergy Asthma Immunol* 2005;94:366-71.
8. Shapiro GS, Yegen Ü, Xiang J, Kottakis J, Cioppa GD. A randomized, double-blind, single dose, crossover clinical trial of the onset and duration of protection from exercise-induced bronchoconstriction by formoterol and albuterol. *Clin Ther* 2002;24:2077-87.
9. Nelson JA, Strauss L, Skowronski M, Ciufo R, Novak R, McFadden ER. Effect of long-term salmeterol treatment on exercise-induced asthma. *N Eng J Med* 1998;339:141-6.
10. Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997;99:655-9.
11. Anderson SD, Brannon JD. Long-acting β_2 -adrenoceptor agonists and exercise-induced asthma: lessons to guide us in the future. *Pediatr Drugs* 2004;6:161-75.
12. Taylor DR. β -adrenergic receptor polymorphisms: relationship to the β -agonist controversy and clinical implications. *Expert Opin Pharmacother* 2007;8:3195-203.
13. Taylor DR, Hall IP. ADRB2 polymorphisms and β_2 agonists. *Lancet* 2007;370:2075-6.
14. Weinberger M, Abu-Hasan M. Life threatening asthma during treatment with salmeterol. *N Engl J Med* 2006;335:852-3.
15. Kindermann W. Do inhaled β_2 agonists have an ergogenic potential in non-asthmatic competitive athletes? *Sports Med* 2007;37:95-102.

Correction

With regard to the July 2008 article entitled "HIV/AIDS: Waiting for a cure" (*J Allergy Clin Immunol* 2008;122:34-5), in 2 locations in the text and in the reference list, the surname of Dr Robert F. Siliciano was misspelled as "Siciliano." The publisher regrets this error.