

Adverse effects of β -agonists

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Short-acting β -adrenergic receptor agonists have pharmacologically predictable dose-related and potency-related adverse effects, including tachycardia and tremor, and they also affect serum potassium and glucose. These effects all show tolerance with continued exposure. The potential for arrhythmia is increased by comorbidity and hypoxemia. Nonpharmacologically predictable effects include airway hyperresponsiveness to nonspecific and specific stimuli, including allergen and exercise, and increased airway inflammation. Genetic variants of the β -adrenergic receptor alter susceptibility to adverse effects of β -agonists on airway function. The impact of the enantiomers of β -agonists on adverse effects remains unclear. The two epidemics of asthma death among young people were temporally associated with introduction of potent short-acting β -agonists (isoproterenol and fenoterol) and appear to be related to adverse effects of these drugs on airway function and airway hyperresponsiveness rather than to cardiotoxicity. Compared with short-acting agents, long-acting β -agonists show similar but less pronounced pharmacologically predictable effects, and they have not been shown to increase airway hyperresponsiveness in adults. Postmarketing surveillance studies have not suggested significant adverse effects of long-acting β -agonists on morbidity and mortality. (*J Allergy Clin Immunol* 2002;110:S322-8.)

Key words: Airway responsiveness, asthma mortality, β -agonist, cardiotoxicity, inflammation

β -Adrenergic receptor (β AR) agonists have been used to treat asthma for more than a century. As β_2 AR-specific drugs have been formulated, adverse effects, particularly those that are pharmacologically predictable because of the "adrenaline-like" stimulation of both α ARs and β ARs, have become less problematic. However, other adverse effects have been observed that were not pharmacologically predictable, such as airway hyperresponsiveness (AHR) and perhaps increased inflammation, and the implication of these effects has been vigorously debated. This article reviews the known and suspected adverse effects of β -agonists in these two broad categories, first for short-acting β -agonists (SABAs) and then for long-acting β -agonists (LABAs).

Abbreviations used

AHR: Airway hyperresponsiveness
 β AR: β -Adrenergic receptor
COPD: Chronic obstructive pulmonary disease
LABA: Long-acting β -agonist
MDI: Metered-dose inhaler
SABA: Short-acting β -agonist

PHARMACOLOGICALLY PREDICTABLE EFFECTS OF SABAs

Cardiac effects

Mild tachycardia is common when patients are first exposed to β -agonists, even the most recent highly β_2 AR-specific agents. In part, tachycardia may result from dilation of peripheral vasculature that reduces venous return, resulting in sympathetic nervous system reflexes and increased inotropic and chronotropic effects. β -Agonists may also stimulate β_2 ARs in the cardiac muscle itself, in both the left ventricle and the right atrium, increasing heart rate directly.

The early adrenergic agents, such as isoproterenol and epinephrine, all predictably increased heart rate.¹ Increases in heart rate occur more significantly with fenoterol than with albuterol²⁻⁵ or terbutaline^{4,6} and are dose-related^{4,5,7-10} for all agents. Fenoterol has been reported to be as potent as isoproterenol in causing tachycardia.¹¹ In one study, increases in heart rate after high doses of fenoterol, albuterol, and terbutaline were, respectively, +29, +8, and +8 bpm.⁴ Fortunately, tolerance develops rapidly to the cardiac-stimulating effects of β_2 -agonists,⁸ even to high-dose isoproterenol.¹² Very few patients have tachycardia, which is more likely to be seen in infrequent rather than frequent users.

Heart rate increases are reflected in adverse reports of palpitations, but arrhythmias are reported much less often. Rhythm disturbances may occur more frequently with fenoterol than albuterol. In one study,⁵ 4 of 15 patients had ventricular arrhythmias with fenoterol but none with albuterol, again in a dose-related manner. Terbutaline use by patients with chronic obstructive pulmonary disease (COPD) resulted in ectopic activity but no frank arrhythmias.¹³ Measurable changes can be recorded in electrocardiographic parameters, such as the QTc interval and the Q-S₂ interval, and in blood pressure,² but the clinical significance of these changes is still being debated. Rare case reports of troublesome arrhythmias suggest that some subjects may have a low threshold for ventricular arrhythmias even in the absence of a prolonged QTc interval.¹⁴ The inotropic and chronotropic effects of fenoterol (increased rate, increased systolic blood pressure, and decreased Q-S₂ interval) may be potentiated by theophylline.¹⁵

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The role of the aerosol propellant rather than the β_2 -agonist itself in causing cardiac adverse effects was suggested by animal studies. Mice, rats, and dogs inhaling fluorocarbon propellants became sensitive to asphyxia-induced bradycardia, atrioventricular block, and T-wave depression; these agents have a rapid, prolonged, and often lethal effect.¹⁶ However, there is very little evidence in human beings to support a role for propellants in causing cardiac disturbances. Some patients may have paradoxical bronchoconstriction from additives in metered-dose inhalers (MDI) and benefit from use of propellant-free β -agonists.¹⁷

Other reports have linked β -agonists with cardiac ischemia, heart failure, and cardiomyopathy. These range from small case series, such as induction of angina in subjects using nebulized albuterol,¹⁸ to single case reports of fatal myocardial necrosis after intravenous isoproterenol¹⁹ or of prolonged but reversible myocardial depression with high-dose isoproterenol and albuterol.²⁰ A case-control study reported a relation between idiopathic dilated cardiomyopathy and β_2 -agonist use (20.0% of cases vs 6.7% of control subjects had used β_2 -agonists), but the relation was uncertain, especially since there was no relation to the duration of β_2 -agonist use.²¹

In the 1960s and early 1970s, there was an epidemic of asthma deaths in the United Kingdom, Australia, and New Zealand—countries using a high-dose formulation of isoproterenol (5 times higher dose per puff). The epidemic was attributed to increased cardiac mortality rates, but a second epidemic in New Zealand and related investigations²² suggest a different cause, as discussed in this report under “Consequences of adverse effects of SABAs.”

An Australian study showed that blood concentrations of albuterol were 2.5 times higher in fatal cases than in hospitalized control subjects with asthma, which may indicate an increased risk caused by β -agonist cardiac toxicity or may simply reflect greater use of albuterol in a more severe, life-threatening (in the end, fatal) attack.²³ The concern that β -agonists in high doses increase asthma mortality rates through cardiac adverse events has not been fully disproved.

Some studies have found no detectable effects of β_2 -agonists on cardiac function (rate, rhythm, or electrocardiography results) by Holter monitoring in children²⁴ and adults, including those with COPD who were also using theophylline or who also had heart disease.²⁵ Arrhythmias occurred in these patients, including supraventricular tachycardia, atrial fibrillation, paroxysmal atrial fibrillation, and ventricular ectopic beats, but they were not aggravated by theophylline.

On the other hand, larger epidemiologic studies have indicated an increased risk of cardiac events. Death in patients with COPD in Saskatchewan was related to use of oral and nebulized β_2 -agonists as opposed to MDI administration.²⁶ A recent case-control study in Seattle, Washington, revealed a dose-related increased risk of acute coronary events related to β -agonist prescriptions after adjustment for age and cardiovascular risk factors, including hypertension, diabetes, and smoking history.²⁷

In subjects not given β -blockers, the adjusted odds ratio for acute coronary events was 1.55 (95% CI, 0.60 to 3.99) for patients who had used 1 to 2 MDI canisters in the last 90 days, 4.07 for those who had used 3 to 5 canisters (95% CI, 2.17 to 7.64), and 3.83 (95% CI, 2.02 to 7.29) for those who had used 6 or more canisters.

Tremor

The incidence of tremor is low with the use of β -agonists and is more likely to be seen with oral therapy than with inhaled therapy. Tremor develops from an imbalance between the fast- and slow-twitch muscle groups of the extremities, and its severity varies greatly between individuals. As is true of cardiac events, tremor is a dose-related, pharmacologically predictable phenomenon seen in both normal subjects and asthmatic persons.^{4,7,8,10} Tolerance develops with continued use.^{8,13} The more potent full agonist fenoterol is more likely to produce tremor than albuterol or terbutaline.⁴

Metabolic effects

Numerous studies have shown that the serum potassium level decreases with the use of inhaled or intravenous β -agonists. This reduction represents an intracellular shift of potassium rather than loss from the body. The shift in potassium is considered to be caused by stimulation of β ARs linked to the membrane-bound Na,K-ATPase on skeletal muscle, which causes an influx of potassium into the cells. Decreased serum potassium is aggravated by the use of corticosteroids and diuretics,²⁸ and the cardiac implications of hypokalemia may be aggravated by hypoxia. Hence, in situations of life-threatening asthma, there may be an increased risk of cardiac abnormalities associated with hypokalemia in the presence of corticosteroids and hypoxia.

The decrease in serum potassium is dose-related⁷ and potency-related, with fenoterol having a more profound hypokalemic effect than albuterol or formoterol² or terbutaline.⁴ In the latter study, mean decreases in serum potassium (SD) with high doses of fenoterol, albuterol, and terbutaline (26 puffs over 4 to 5 hours) were, respectively, -0.76 (0.62), -0.46 (0.32), and -0.52 (0.39) mmol/L.⁴ As with other pharmacologically predictable effects, tolerance has been demonstrated with repeated use.^{8,13}

β -Agonists increase glycogenolysis and hence increase plasma glucose.⁷ This is of minor importance, except in diabetic patients, whose disease is likely to be aggravated by the use of systemic corticosteroids in situations of severe asthma. The effect on glucose also shows tolerance with repeated use.^{8,13}

PHARMACOLOGICALLY PREDICTABLE EFFECTS OF SABAs IN UNUSUAL PHYSIOLOGIC CIRCUMSTANCES

Several research groups have quite extensively studied the effects of hypoxia in an acute episode of asthma on the response of cardiac muscle and the intact cardiac function as evaluated by electrocardiography. Such

effects, which could exaggerate the adverse effects of β -agonists, imply that hypoxemia and hypercapnia should be aggressively treated when high doses of β -agonists are required in acute situations and that perhaps β -agonists should be used with caution in patients with chronic hypoxia and hypercapnia.

Normal male subjects exposed to hypoxic conditions showed cardiac effects from fenoterol, measured as increases in heart rate, systolic blood pressure, stroke volume, cardiac index, ejection fraction, and QTc interval and decreases in Q-S₂ interval and diastolic blood pressure. Some effects were additive; for example, hypoxia alone increased heart rate by 8.0 bpm, fenoterol alone increased it by 14.3 bpm, and fenoterol under hypoxic conditions increased it by 21.9 bpm.²⁹ One mechanism by which hypoxia may aggravate the cardiotoxic effects of β_2 -agonists is by increasing peripheral vasodilation.³⁰ Subjects exposed to hypoxemia showed a 45% increase in forearm blood flow ($P = .001$), although in that study there were no measurable effects on blood pressure, QTc interval, or potassium shifts. However, in acute asthma, such changes in peripheral resistance might increase the propensity for cardiac adverse effects.³¹ Little is known of the effects of hypercapnia on cardiac adverse effects.

NONPHARMACOLOGICALLY PREDICTABLE EFFECTS OF SABAs

Increased nonspecific airway responsiveness

Several carefully conducted studies have confirmed that the regular or frequent use of the classic SABAs fenoterol, albuterol, and terbutaline can result in a small increase in AHR, measurable after the drug is withheld for some hours. Responsiveness to nonspecific bronchoconstrictor agents such as histamine or methacholine was increased between 0.5 and 1 doubling dilution by regular use of β -agonist in the majority of studies reviewed.

Animal studies have shown AHR to histamine after treatment with isoproterenol and other β -agonists.³² Differences in AHR between children treated with terbutaline and inhaled corticosteroid were noted by Kraan et al,³³ who raised the possibility of an adverse effect of β_2 -agonists. In a year-long, randomized, placebo-controlled, crossover study of regular versus as-needed β -agonists, a difference of 0.5 doubling dilution response to methacholine was observed (greater AHR with regular fenoterol).³⁴ Drazen et al³⁵ observed a similar effect with regular albuterol in subjects with milder disease, although later in the study the statistically significant (0.5 doubling dilution) increase in AHR to methacholine decreased somewhat to become nonsignificant. Van Schayck et al³⁶ showed increased AHR to histamine with regular use of albuterol QID and excluded receptor subsensitization as a cause for this. Bhagat et al³⁷ showed that the effect of a β_2 -agonist on AHR was significant with the highest dose of the β_2 -agonist, but effects with lower doses were not significant. Regular use of albuterol was associated with a decrease in protective effect on

adenosine monophosphate challenge.³⁸ The adverse effect of β_2 -agonists on AHR may be more evident with one challenge than another³⁹; for example, increased saline responsiveness but not increased methacholine responsiveness was evident in patients with rhinitis after 4 weeks of regular albuterol.

Of more importance is AHR to specific challenges encountered by the patient, especially allergen and exercise. In a series of related studies, Cockcroft et al⁴⁰ demonstrated an increased early response of β_2 -agonist on allergen challenge and showed that this was a dose-related effect.³⁷ Oral terbutaline also increased the early asthmatic response when it was given orally (7.5 mg slow release BID) and patients were challenged 12 and 48 hours after the last dose.⁴¹ In a study of budesonide and terbutaline, separately and in combination, subjects ($n = 37$ evaluable) were given budesonide 800 μ g BID, terbutaline 1000 μ g TID, both, or double placebo and were subjected to a 3-dose allergen challenge.⁴² The use of terbutaline diminished the bronchoprotective efficacy of budesonide against allergen challenge compared with the effect of budesonide alone.

Regular use of albuterol for 1 week (200 μ g QID) increased the asthmatic response to exercise.⁴³ In the recovery phase, administration of 100 μ g, 100 μ g, and 200 μ g albuterol at 5-minute intervals was associated with a blunted response in those who had used albuterol regularly. This suggests that regular SABA use may lead to a reduced response to emergency bronchodilator treatment during an attack.

The clinical implication of AHR is increased lability of the airways, leading to the possibility of increased airway narrowing on stimulation, and the requirement for higher doses of therapy to maintain control.

Increased inflammation

The use of a regular β_2 -agonist for 7 days has been shown to have an adverse effect on the late asthmatic response to allergen (Fig 1).^{44,45} Evidence of an increased inflammatory response to allergen was noted with increased sputum eosinophils ($P = .005$) and sputum eosinophilic cationic protein ($P = .04$) at 7 hours after challenge (Fig 2).⁴⁵ Similar findings were seen after a 10-day treatment period, with an increased early asthmatic response and increased serum tryptase levels at 1 hour after challenge and an increase in sputum eosinophils (39% vs 5%), increased metachromatic cells, and a lower FEV₁ at 7 hours after challenge.⁴⁶ These results suggest that regular β_2 -agonist use increased allergen responses (early and late) with increased mediator release (increased mast cell degranulation by allergen), implying that β_2 -agonists may potentiate allergic inflammation in the airway. On the other hand, 30 patients with rhinitis given a regular β_2 -agonist for 4 weeks had no change in sputum eosinophils, mast cells, or AHR to methacholine.³⁹

Genetic influence on adverse effects

The adverse effects of β -agonists on lung function and airway responsiveness have been shown in some studies

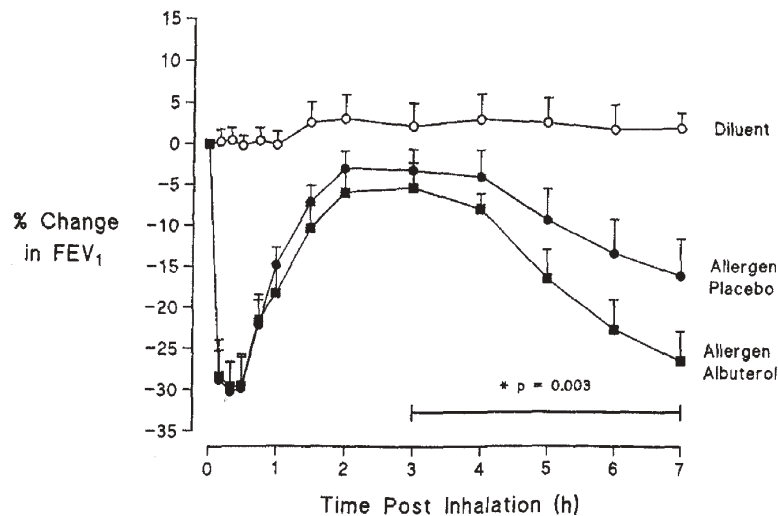


FIG 1. Regular inhaled albuterol increased allergen-induced late response manifested by a greater fall in FEV₁. (From Gauvreau GM, Jordana M, Watson RM, et al. Effect of regular inhaled albuterol on allergen-induced late responses and sputum eosinophils in asthmatic subjects. *Am J Respir Crit Care Med* 1997;156:1738-45. With permission.)

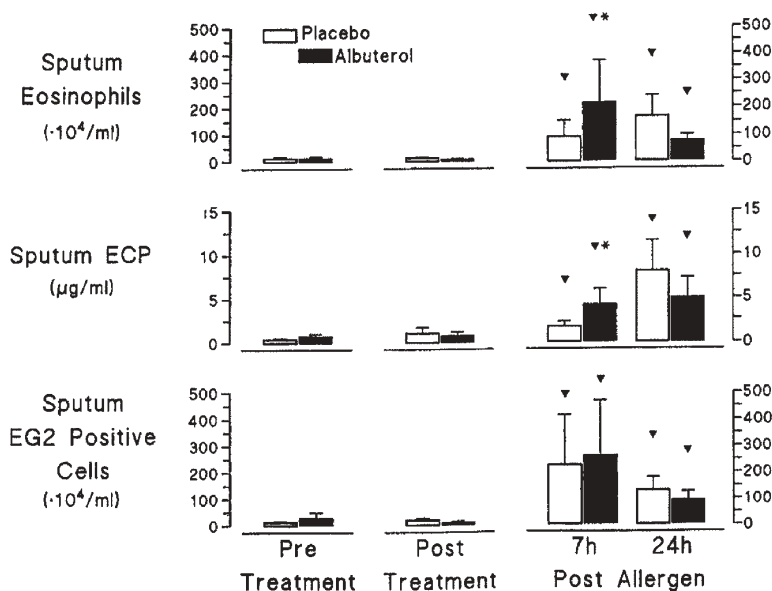


FIG 2. Regular inhaled albuterol increased sputum eosinophils, ECP, and EG2-positive cells (activated eosinophils). (From Gauvreau GM, Jordana M, Watson RM, et al. Effect of regular inhaled albuterol on allergen-induced late responses and sputum eosinophils in asthmatic subjects. *Am J Respir Crit Care Med* 1997;156:1738-45. With permission.)

to be a function of the β AR genotype. Polymorphisms of the β -receptor at codons 16 and 27 are associated with different responses to regular albuterol and possibly to other inhaled β -agonists, although not all studies have been able to demonstrate these relations. In a study by Israel et al,⁴⁷ deterioration in lung function with regular albuterol was observed most clearly in patients with Arg/Arg at codon 16 of the β AR. Subjects with Gly/Gly or heterozygotes did not show a deleterious effect of regular albuterol (Fig 3).

Enantiomers of β_2 -agonists

The impact of the R- and S-enantiomers of β -agonists on airway responsiveness has been debated and remains an area of uncertainty. In animal studies, S-albuterol caused AHR to histamine.⁴⁸ Clinical studies have suggested either no adverse effect of S-isomers of β -agonists or a small negative effect on lung function.⁴⁹ Administration of the R-isomer alone may provide greater clinical efficacy with fewer adverse effects, but further studies are needed to

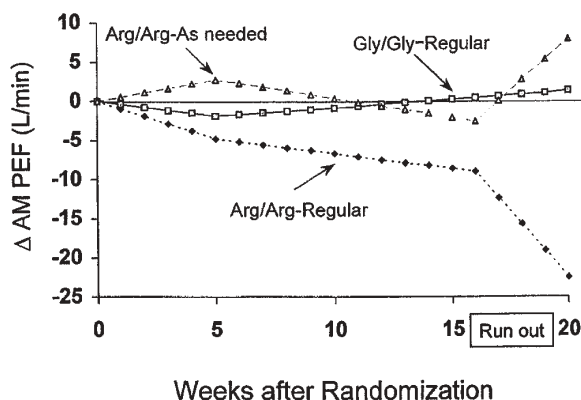


FIG 3. Effect of β_2 AR polymorphisms on response to β_2 -agonists. A deleterious effect of regular albuterol was seen only in subjects with Arg/Arg polymorphisms at codon 16. AM PEF, Morning peak expiratory flow. (From Israel E, Drazen JM, Liggett SB, et al. The effect of polymorphisms of the β_2 -adrenergic receptor on the response to regular use of albuterol in asthma. *Am J Respir Crit Care Med* 2000;162:75-80. With permission.)

clarify this issue.⁵⁰ In one study in children, the use of nebulized levalbuterol had a bronchodilator effect equal to that of a 4-fold higher dose of racemic albuterol, with less effect on heart rate, QTc interval, and glucose, although some effect was still evident on serum potassium.⁵¹

CONSEQUENCES OF ADVERSE EFFECTS OF SABAs

There seems to be little doubt that the epidemics of both mortality and morbidity (as reflected in hospitalizations and emergency room visits) associated with β -agonists are related to adverse effects on airway responsiveness and not to cardiac or metabolic adverse effects. Increased severity of asthma during regular β -agonist treatment has been manifested as lower lung function as well as increased symptoms, nocturnal symptoms, need for short course of prednisone, and other indicators of a more frequent occurrence of exacerbations.^{34,52} During treatment of asthmatic patients with regular fenoterol, 2 puffs QID, the time to the first exacerbation was halved.⁵² Asthma mortality rates increased sharply in New Zealand after the 1976 introduction of high-dose fenoterol (200 μ g per puff).⁵³ A series of case-control studies showed a consistently high risk of death associated with the prescription of fenoterol, both in New Zealand⁵⁴ and in Canada.⁵⁵ There was a marked reduction in asthma mortality rates in New Zealand when fenoterol was withdrawn in 1990.⁵⁶ The parallel decrease in hospitalization for severe asthma in this study provides strong evidence that the adverse effects of fenoterol reflected in mortality rates were not attributable to cardiac arrhythmia, because this would not be reflected in

hospitalizations. Rather, the dramatic response in both morbidity and mortality to withdrawal of a potent β -agonist therapy is consistent with an adverse effect on severity of the disease.²² Excess use of any β -agonist is a risk factor for death, especially when the dose exceeds 1.4 canisters per month.⁵⁷

PHARMACOLOGICALLY PREDICTABLE EFFECTS OF LABAs

The pharmacologically predictable effects of LABAs are similar to those seen with SABAs but overall are less substantial.

Cardiac effects

Kemp et al⁵⁸ found that salmeterol doses from 12.5 to 100 μ g caused only a 2- to 5-bpm increase in heart rate compared with placebo. Of those patients given the higher dose of salmeterol (100 μ g), 13% to 17% of patients had ventricular premature beats (vs 4% to 9% of patients given placebo, albuterol, or lower doses of salmeterol), and 17% of patients given salmeterol 100 μ g reported palpitations. Holter monitoring and echocardiograms of 17 children given 200 μ g salmeterol daily did not show any cardiac adverse effects.⁵⁹ Studies in normal and asthmatic adults with Holter monitoring used likewise have not given cause for concern.^{60,61} The dose-response effect of salmeterol on heart rate was steeper than that of albuterol, suggesting a narrower therapeutic window.⁶² With respect to the effect on the QTc interval, salmeterol had a relative potency of 7.1 (95% CI, 3.9 to 14.4) compared with albuterol. In an emergency room study, high doses of formoterol (total dose, 90 μ g) had less effect than terbutaline (total dose, 10 mg) on heart rate and serum potassium.⁶³ The mean heart rate response was 93.5 versus 101.7 bpm, and serum potassium decreased from 4.02 to 3.89 mg/L versus 4.22 to 3.76 mg/L.

There may be increased risks of LABAs in patients with COPD. Both formoterol and salmeterol induced cardiac effects in patients with COPD, together with a decrease in serum potassium compared with placebo.⁶⁴ These effects could potentially be more problematic in the presence of hypoxemia.

Tremor

Salmeterol can induce a dose-related tremor.^{58,65,66} Of subjects given 100 μ g salmeterol, 21% reported tremor, compared with 12.5% of those given 50 μ g.⁵⁸ Other studies have shown that salmeterol causes less tremor than albuterol.⁶⁵

Metabolic effects

Comparative studies of salmeterol and albuterol have suggested a relative dose potency of salmeterol with respect to effects on serum potassium of 8.2 (95% CI, 5.7 to 12.6).⁶² Very high doses of formoterol can induce serum potassium changes, but these are not of clinical significance⁶⁷ and generally are of smaller magnitude than those induced by SABAs.⁶⁸

NONPHARMACOLOGICALLY PREDICTABLE EFFECTS OF LABAs

Neither salmeterol nor formoterol has been shown to increase airway responsiveness to either specific stimuli (allergen or exercise) or nonspecific stimuli (histamine, methacholine, saline), except in children, in whom the use of salmeterol as monotherapy led to deterioration of lung function and to AHR.^{69,70} Tolerance to the bronchoprotective effects of both salmeterol and formoterol has been repeatedly demonstrated,^{71,72} but rebound AHR has not been shown.⁷³ There is no epidemiologic evidence of any shift in asthma severity associated with the increasing use of salmeterol or formoterol, although the postmarketing surveillance study of salmeterol in the United Kingdom did document a nonsignificant increase in the relative risk for death to 3.0 ($P = .10$).⁷⁴ Subsequent pharmacoepidemiologic studies in the United Kingdom have not demonstrated any major concern with the use of salmeterol,⁷⁵ and no concerns of this nature have been raised with formoterol. In the United Kingdom, prescription event monitoring in 15,407 patients over a period of 1 year recorded 1022 deaths, including 73 deaths of asthmatic patients, 39 of whom had been using salmeterol in the last month of life.⁷⁵ All died of natural causes, but in 4 of the 39 (10%), the temporal association raised the possibility of a causal relation.

CONCLUSIONS

In summary, the pharmacologically predictable effects of both SABAs and LABAs are not problematic, except perhaps in the presence of hypoxia or comorbidity, and tolerance to these effects occurs readily. LABAs overall show fewer pharmacologically predictable effects than SABAs. Adverse effects on airway responsiveness and inflammation have been shown with regular SABAs but not with LABAs.

DISCUSSION SESSION

Question: In the United States, patients with COPD are being switched to nebulized albuterol as opposed to regular long-acting bronchodilators because Medicare regulations allow a payment for that. Did you see differences between nebulized albuterol versus metered-dose inhalers?

Dr Sears: I think overall, if you consider all of the studies, regular long-acting β -agonists are much better than frequent short-acting β -agonists. The safety data for the long-acting β -agonists are really very good.

Question: What caused the deaths in New Zealand?

Dr Sears: I believe that what happened was that when fenoterol was launched, we used it particularly in patients with troublesome asthma, quite unaware that we were unknowingly increasing airway responsiveness. I think the whole epidemic is due to increased severity of disease and not to cardiac effects. Asthma mortality decreased substantially when fenoterol was withdrawn. However, the hospital admission rate also declined by 50% in 1 year when patients were switched back to albuterol. This speaks very strongly for the fact that asthma severity was driving the phenomenon. Patients were dying of status asthmaticus caused by airway hyper-responsiveness with short-acting β -agonist treatment.

REFERENCES

1. Riding WD, Dinda P, Chatterjee SS. The bronchodilator and cardiac effects of five pressure-packed aerosols in asthma. *Br J Dis Chest* 1970;64:37-45.
2. Bremner P, Woodman K, Burgess C, et al. A comparison of the cardiovascular and metabolic effects of formoterol, salbutamol and fenoterol. *Eur Respir J* 1993;6:204-10.
3. Bremner P, Burgess C, Beasley R, et al. Nebulized fenoterol causes greater cardiovascular and hypokalaemic effects than equivalent bronchodilator doses of salbutamol in asthmatics. *Respir Med* 1992;86:419-23.
4. Wong CS, Pavord ID, Williams J, et al. Bronchodilator, cardiovascular, and hypokalaemic effects of fenoterol, salbutamol, and terbutaline in asthma. *Lancet* 1990;336:1396-9.
5. Tandon MK. Cardiopulmonary effects of fenoterol and salbutamol aerosols. *Chest* 1980;77:429-31.
6. Gray BJ, Frame MH, Costello JF. A comparative double-blind study of the bronchodilator effects and side effects of inhaled fenoterol and terbutaline administered in equipotent doses. *Br J Dis Chest* 1982;76:341-50.
7. Lipworth BJ, McDevitt DG. Beta-adrenoceptor responses to inhaled salbutamol in normal subjects. *Eur J Clin Pharmacol* 1989;36:239-45.
8. Lipworth BJ, Struthers AD, McDevitt DG. Tachyphylaxis to systemic but not to airway responses during prolonged therapy with high dose inhaled salbutamol in asthmatics. *Am Rev Respir Dis* 1989;140:586-92.
9. Vathenen AS, Britton JR, Ebdon P, et al. High-dose inhaled albuterol in severe chronic airflow limitation. *Am Rev Respir Dis* 1988;138:850-5.
10. Lipworth BJ, Clark RA, Dhillon DP, et al. β -Adrenoceptor responses to high doses of inhaled salbutamol in patients with bronchial asthma. *Br J Clin Pharmacol* 1988;26:527-33.
11. Crane J, Burgess C, Beasley R. Cardiovascular and hypokalaemic effects of inhaled salbutamol, fenoterol, and isoprenaline. *Thorax* 1989;44:136-40.
12. Paterson JW, Connolly ME, Davies DS, et al. Isoprenaline resistance and the use of pressurised aerosols in asthma. *Lancet* 1968;2:426-9.
13. Lipworth BJ, Clark RA, Dhillon DP, et al. Comparison of the effects of prolonged treatment with low and high doses of inhaled terbutaline on beta-adrenoceptor responsiveness in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis* 1990;142:338-42.
14. Finn AF, Thompson CM, Banov CH, et al. Beta₂-agonist induced ventricular dysrhythmias secondary to hyperexcitable conduction system in the absence of a long QT syndrome. *Ann Allergy Asthma Immunol* 1997;78:230-2.
15. Flatt A, Burgess C, Windom H, et al. The cardiovascular effects of inhaled fenoterol alone and during treatment with oral theophylline. *Chest* 1989;96:1317-20.
16. Taylor GJ IV, Harris WS. Cardiac toxicity of aerosol propellants. *JAMA* 1970;214:81-5.
17. Selroos O, Löfroos A-B, Pietinalho A, et al. Comparison of terbutaline and placebo from a pressurised metered dose inhaler and a dry powder inhaler in a subgroup of patients with asthma. *Thorax* 1994;49:1228-30.
18. Neville E, Corris PA, Vivian J, et al. Nebulised salbutamol and angina. *Br Med J* 1982;285:796-7.
19. Kurland G, Williams J, Lewiston NJ. Fatal myocardial toxicity during continuous infusion intravenous isoproterenol therapy of asthma. *J Allergy Clin Immunol* 1979;63:407-11.
20. Raper R, Fisher M, Bihari D. Profound, reversible, myocardial depression in acute asthma treated with high-dose catecholamines. *Crit Care Med* 1992;20:710-2.
21. Coughlin SS, Metayer C, McCarthy EP, et al. Respiratory illness, β -agonists, and risk of idiopathic dilated cardiomyopathy. The Washington, DC, Cardiomyopathy Study. *Am J Epidemiol* 1995;142:395-403.
22. Sears MR, Taylor DR. The β_2 -agonist controversy: observations, explanations and relationship to asthma epidemiology. *Drug Safety* 1994;11:259-83.
23. Abramson MJ, Bailey MJ, Couper FJ, et al. Are asthma medications and management related to deaths from asthma? *Am J Respir Crit Care Med* 2001;163:12-8.
24. Katz RW, Kelly HW, Crowley MR, et al. Safety of continuous nebulized albuterol for bronchospasm in infants and children. *Pediatrics* 1993;92:666-9.
25. Poukkula A, Korhonen UR, Huikuri H, et al. Theophylline and salbutamol in combination in patients with obstructive pulmonary disease and concurrent heart disease: effect on cardiac arrhythmias. *J Intern Med* 1989;226:229-34.

26. Suissa S, Hemmelgarn B, Blais L, et al. Bronchodilators and acute cardiac death. *Am J Respir Crit Care Med* 1996;154:1598-602.
27. Au DH, Curtis JR, Every NR, et al. Association between inhaled β -agonists and the risk of unstable angina and myocardial infarction. *Chest* 2002;121:846-51.
28. Lipworth BJ, McDevitt DG, Struthers AD. Prior treatment with diuretic augments the hypokalemic and electrocardiographic effects of inhaled albuterol. *Am J Med* 1989;86:653-7.
29. Bremner P, Burgess CD, Crane J, et al. Cardiovascular effects of fenoterol under conditions of hypoxaemia. *Thorax* 1992;47:814-7.
30. Burggraaf J, Wesstendorp RGJ, in't Veen JCCM, et al. Cardiovascular side effects of inhaled salbutamol in hypoxic asthmatic patients. *Thorax* 2001;56:567-9.
31. Lipworth BJ. Revisiting interactions between hypoxaemia and β_2 agonists in asthma. *Thorax* 2001;56:506-7.
32. Galland BC, Blackman JG. Enhancement of airway reactivity of histamine by isoprenaline and related β -adrenoceptor agonists in the guinea-pig. *Br J Pharmacol* 1993;108:1016-23.
33. Kraan J, Koëter GH, van der Mark ThW, 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.
34. Sears MR, Taylor DR, Print CG, et al. Regular inhaled beta-agonist treatment in bronchial asthma. *Lancet* 1990;336:1391-6.
35. 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.
36. van Schayck CP, Graafma SJ, Visch MB, et al. Increased bronchial hyperresponsiveness after inhaled salbutamol during 1 year is not caused by subsensitization to salbutamol. *J Allergy Clin Immunol* 1990;86:793-800.
37. Bhagat R, Swystun VA, Cockcroft DW. Salbutamol-induced increased airway responsiveness to allergen and reduced protection versus methacholine: dose response. *J Allergy Clin Immunol* 1996;97:47-52.
38. Jokic R, Swystun VA, Davis BE, et al. Regular inhaled salbutamol: effect of airway responsiveness to methacholine and adenosine 5'-monophosphate and tolerance to bronchoprotection. *Chest* 2001;119:370-5.
39. Evans DW, Salome CM, King GG, et al. Effect of regular inhaled salbutamol on airway responsiveness and airway inflammation in rhinitic non-asthmatic subjects. *Thorax* 1997;52:136-42.
40. Cockcroft DW, McParland CP, Britto SA, et al. Regular inhaled salbutamol and airway responsiveness to allergen. *Lancet* 1993;342:833-7.
41. Larsson K, Martinsson A, Hjemdahl P. Influence of β -adrenergic receptor function during terbutaline treatment on allergen sensitivity and bronchodilator response to terbutaline in asthmatic subjects. *Chest* 1992;101:953-60.
42. Wong CS, Wahedna I, Pavord ID, et al. Effect of regular terbutaline and budesonide on bronchial reactivity to allergen challenge. *Am J Respir Crit Care Med* 1994;150:1268-73.
43. Hancox RJ, Subbarao P, Kamada D, et al. β_2 -Agonist tolerance and exercise-induced bronchospasm. *Am J Respir Crit Care Med* 2002;165:1068-70.
44. Cockcroft DW, O'Byrne PM, Swystun VA, et al. Regular use of inhaled albuterol and the allergen-induced late asthmatic response. *J Allergy Clin Immunol* 1995;96:44-9.
45. Gauvreau GM, Jordana M, Watson RM, et al. Effect of regular inhaled albuterol on allergen-induced late responses and sputum eosinophils in asthmatic subjects. *Am J Respir Crit Care Med* 1997;156:1738-45.
46. Swystun VA, Gordon JR, Davis EB, et al. Mast cell tryptase release and asthmatic responses to allergen increase with regular use of salbutamol. *J Allergy Clin Immunol* 2000;106:57-64.
47. 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.
48. Mazzoni L, Naef R, Chapman ID, et al. Hyperresponsiveness of the airways following exposure of guinea-pigs to racemic mixtures and distomers of β_2 -selective sympathomimetics. *Pulm Pharmacol* 1994;7:367-76.
49. Ind PW. Salbutamol enantiomers: early clinical evidence in humans. *Thorax* 1997;52:839-40.
50. Nelson HS. Clinical experience with levalbuterol. *J Allergy Clin Immunol* 1999;104:S77-84.
51. Milgrom H, Skoner DP, Bensch G, et al. Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. *J Allergy Clin Immunol* 2001;108:938-45.
52. Taylor DR, Sears MR, Herbison GP, et al. Regular inhaled β -agonist in asthma: effect on exacerbations and lung function. *Thorax* 1993;48:134-8.
53. Pearce N, Beasley R, Crane J, et al. End of the New Zealand asthma mortality epidemic. *Lancet* 1995;345:41-4.
54. Crane J, Burgess C, Pearce N, et al. The β -agonist controversy: a perspective. *Eur Respir Rev* 1993;3:475-82.
55. 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.
56. Sears MR. Epidemiological trends in asthma. *Can Respir J* 1996;3:261-8.
57. Suissa S, Ernst P, Boivin J-F, et al. A cohort analysis of excess mortality in asthma and the use of inhaled β -agonists. *Am J Respir Crit Care Med* 1994;149:604-10.
58. Kemp JP, Bierman CW, Cocchetto DM. Dose-response study of inhaled salmeterol in asthmatic patients with 24-hour spirometry and Holter monitoring. *Ann Allergy* 1993;70:316-22.
59. Tunaoglu TS, Turktas I, Olgunturk R, et al. Cardiac side effects of long-acting beta-2 agonist salmeterol in asthmatic children. *Pediatr Int* 1999;41:28-31.
60. Tranfa CME, Pelaia G, Grembale RD, et al. Short-term cardiovascular effects of salmeterol. *Chest* 1998;113:1272-6.
61. Chervinsky P, Goldberg P, Galant S, et al. Long-term cardiovascular safety of salmeterol powder pharmacotherapy in adolescent and adult patients with chronic persistent asthma. *Chest* 1999;115:642-8.
62. Bennett JA, Tattersfield AE. Time course and relative dose potency of systemic effects from salmeterol and salbutamol in healthy subjects. *Thorax* 1997;52:458-64.
63. Malolepszy J, Böszörményi Nagy G, Selroos O, et al. Safety of formoterol Turbuhaler at cumulative dose of 90 μ g in patients with acute bronchial obstruction. *Eur Respir J* 2001;18:928-34.
64. Cazzalo M, Imperatore F, Salzillo A, et al. Cardiac effects of formoterol and salmeterol in patients suffering from COPD with preexisting cardiac arrhythmias and hypoxemia. *Chest* 1998;114:411-5.
65. Lötvall J, Lunde H, Svedmyr N. Onset of bronchodilation and finger tremor induced by salmeterol and salbutamol in asthmatic patients. *Can Respir J* 1998;5:191-4.
66. Bronsky EA, Kemp JP, Orgel HA, et al. A 1-week dose-ranging study of inhaled salmeterol in patients with asthma. *Chest* 1994;105:1032-7.
67. Maesen FPV, Costongs R, Smeets JJ, et al. The effect of maximal doses of formoterol and salbutamol from a metered dose inhaler on pulse rates, ECG, and serum potassium concentrations. *Chest* 1991;99:1367-73.
68. Rabe KF. Formoterol in clinical practice: safety issues. *Respir Med* 2001;95:S21-5.
69. Verberne AAPH, Frost C, Roorda RJ, et al. One year treatment with salmeterol compared with beclomethasone in children with asthma. *Am J Respir Crit Care Med* 1997;156:688-95.
70. Simons FER, and the Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *N Engl J Med* 1997;337:1659-65.
71. Cheung D, Timmers MC, Zwinderman AH, et al. 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.
72. Grootendorst DC, Sterk PJ, Heijerman HGM. Effect of oral prednisolone on the bronchoprotective effect of formoterol in patients with persistent asthma. *Eur Respir J* 2001;17:374-9.
73. Meijer GG, Postma DS, Mulder PGH, et al. Long-term circadian effects of salmeterol in asthmatic children treated with inhaled corticosteroids. *Am J Respir Crit Care Med* 1995;152:1887-92.
74. Castle W, Fuller R, Hall J, et al. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *Br Med J* 1993;306:1034-7.
75. Mann RD, Kubota K, Pearce G, et al. Salmeterol: a study by prescription-event monitoring in a UK cohort of 15,407 patients. *J Clin Epidemiol* 1996;49:247-50.