REVIEW ARTICLE

DRUG THERAPY
ALASTAIR J.J. WOOD, M.D., Editor

β-ADRENERGIC BRONCHODILATORS
HAROLD S. NELSON, M.D.

Of the three classes of bronchodilators (β₂-adrenergic–receptor agonists, methylxanthines, and anticholinergic agents), the β₂-adrenergic–receptor agonists produce the greatest bronchodilation in patients with bronchial asthma.1 β₂-Adrenergic agonists are generally preferred both for the relief of acute symptoms2,3 and for the prevention of exercise-induced bronchospasm.4 The recent introduction of long-acting inhaled β₂-adrenergic agonists has overcome the principal shortcoming of the previously available drugs of this class, their limited duration of action. However, the possibility of adverse effects with regular use of β₂-adrenergic agonists has been raised.2,5 In this article I shall review the pharmacology of the β₂-adrenergic agonists, examine potential adverse effects associated with their use, and discuss their clinical role.

The β₂-Adrenergic Receptor

The adrenergic receptors are classified as predominantly stimulatory α receptors or predominantly inhibitory β receptors. The latter have been subclassified as β₁, β₂, and β₃ receptors. Although both β₂- and β₁-adrenergic receptors are present in the lungs, bronchodilation appears to be entirely a function of β₂-adrenergic receptors.6

β₂-Adrenergic agonists produce their effects through interaction with specific β₂-adrenergic receptors located in the plasma membrane of virtually all types of cell. The receptors consist of a protein that traverses the cell membrane seven times, forming three extracellular and three intracellular loops. The receptor is linked to a stimulatory guanine-nucleotide–binding protein (Gₛ). Occupancy of the β₂-adrenergic receptor changes the conformation of Gₛ, leading to activation of adenylate cyclase, which in turn catalyzes the conversion of adenosine triphosphate (ATP) to cyclic adenosine monophosphate (AMP). Cyclic AMP is responsible for the physiologic response, the nature of which differs with the type of cell.6

A characteristic of many membrane-associated receptors, including β₂-adrenergic receptors, is desensitization after high-dose or repeated exposure to the agonist. There are several mechanisms of desensitization. After only a few minutes of exposure to a β₂-adrenergic agonist, the receptor is phosphorylated, which interferes with its coupling to Gₛ.7 With somewhat more prolonged exposure the receptors are internalized to a region of the cell below the cell surface.8 Finally, with prolonged exposure, the number of receptors in the plasma membrane is reduced, because of decreased production of the messenger RNA (mRNA) for the receptor (down-regulation).9 Up-regulation of the receptor can result from increased production of mRNA due to an increase in the transcription of the gene for the receptor, which is stimulated by glucocorticoid and thyroid hormone.10

Classes of β₂-Adrenergic Agonists

Catecholamine bronchodilators such as isoproterenol and isethamine have been largely replaced as prescription drugs by longer-acting formulations that are not degraded by the enzyme catechol O-methyltransferase.13 Inhalers containing epinephrine are still available without prescription and provide moderate but relatively brief bronchodilation. The β₂-adrenergic agonists commonly used today are listed in Table 1. They may be divided into those with an intermediate duration of action (3 to 6 hours)13 and those that are long-acting, with a duration of action of more than 12 hours.14 Of the intermediate-acting drugs available in the United States, there is little reason to choose one over the others. Metaproterenol is less β₂-adrenergic–specific than other agents and hence more apt to cause cardiac stimulation.15 This is usually not a problem with the customary dose of two inhalations at intervals of four or more hours, but problems may arise if metaproterenol is given in higher doses or more frequently.

The two long-acting β₂-adrenergic bronchodilators have extended side chains (Fig. 1). Both are highly lipophilic and have a high affinity for the β₂-adrenergic receptor. The mechanisms by which their long duration of action is achieved differ.16 The side chain of salmeterol binds to a specific site within the β₂-adrenergic receptor that allows prolonged activation of the receptor.17 Formoterol, on the other hand, appears to enter the plasmalemma lipid bilayer from which it gradually leaches out and is thus available over a prolonged period to stimulate the β₂-adrenergic receptor.18

Routes of Administration

β₂-Adrenergic bronchodilators can be administered orally, by inhalation, or by subcutaneous or intravenous injection. The inhaled route is preferred almost without exception because the side effects are fewer for any given degree of bronchodilatation.19 Inhalation is as effective as parenteral administration for treating acute, severe attacks of asthma in most patients,20 although some who have severe bronchial obstruction may benefit initially from parenteral therapy.21

Oral preparations still have some role in the treatment of children too young to use a metered-dose inhaler conveniently. Sustained-release oral preparations reduce nocturnal asthma,22 but they are not as effective...
The use of a nebulizer to deliver a bronchodilator was formerly standard practice for young children; in the emergency treatment of patients with acute, severe asthmatic; and for the treatment of hospitalized patients. All these indications have been challenged, however, \( \beta_2 \)-Adrenergic therapy delivered under supervision by a metered-dose inhaler with a spacer device is as effective in the emergency setting as therapy with a nebulizer for both adults and children. In hospitalized patients, therapy with metered-dose inhalers is as effective as nebulizer treatments and results in considerable savings. Even in small children, the nebulizer may be replaced by a spacer device with an attached mask.

**Table 1. Representative Inhaled \( \beta \)-Adrenergic Bronchodilators.**

<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>PROPRIETARY NAME*</th>
<th>DOSE†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate-acting (3–6 hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metaproterenol</td>
<td>Alupent, Metaprol</td>
<td>650 ( \mu )g</td>
</tr>
<tr>
<td>Albuterol</td>
<td>Proventil, Ventolin</td>
<td>90 ( \mu )g</td>
</tr>
<tr>
<td>Bitoletol</td>
<td>Tornalate</td>
<td>370 ( \mu )g</td>
</tr>
<tr>
<td>Pirbuterol</td>
<td>Maxair</td>
<td>200 ( \mu )g</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>Brethaire</td>
<td>200 ( \mu )g</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>Not available in U.S.</td>
<td>—</td>
</tr>
<tr>
<td>Long-acting (&gt;12 hr)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Serevent</td>
<td>21 ( \mu )g</td>
</tr>
<tr>
<td>Formoterol</td>
<td>Not available in U.S.</td>
<td>—</td>
</tr>
</tbody>
</table>

*In the United States.
†Dose released from the mouthpiece of the inhaler per activation.

Inhaled \( \beta \)-agonists can be administered as a wet aerosol from a jet or ultrasonic nebulizer, or they can be administered from a metered-dose inhaler either as a propellant-generated aerosol or as a breath-propelled dry powder (Fig. 2). The bronchodilator response to \( \beta_2 \)-adrenergic agonists is log-linear, so that a doubled effect is achieved only by a 10-fold increase in the dose.

The relative efficiencies of the nebulizer and metered-dose inhaler vary with the techniques used for each. With optimal technique (Table 2), approximately 12 percent of the drug is delivered from the metered-dose inhaler to the lung; the remainder is deposited in the mouth, pharynx, and larynx. In general, the dose required in a nebulizer is 6 to 10 times that used in a metered-dose inhaler to produce the same degree of bronchodilation.

The use of a nebulizer to deliver a bronchodilator was formerly standard practice for young children; in the emergency treatment of patients with acute, severe asthma; and for the treatment of hospitalized patients. All these indications have been challenged, however, \( \beta_2 \)-Adrenergic therapy delivered under supervision by a metered-dose inhaler with a spacer device is as effective in the emergency setting as therapy with a nebulizer for both adults and children. In hospitalized patients, therapy with metered-dose inhalers is as effective as nebulizer treatments and results in considerable savings. Even in small children, the nebulizer may be replaced by a spacer device with an attached mask.

**Figure 1. Structure of \( \beta \)-Adrenergic Bronchodilators.**

Illustrated are isoproterenol, a representative short-acting, nonselective \( \beta \)-agonist; albuterol, a \( \beta_2 \)-selective agonist with an intermediate duration of action; and salmeterol and formoterol, long-acting, selective \( \beta_2 \)-agonist bronchodilators. For albuterol, an intermediate duration of action was achieved by altering the catechol configuration of adjacent hydroxyl groups on carbons 3 and 4 of the benzene ring, and increased \( \beta_2 \) selectivity was achieved by adding a methyl group to the nitrogen of the side chain. See the text for a description of the mechanisms of action of the long-acting \( \beta_2 \)-agonists.
in vivo. However, salmeterol did not reduce the urinary excretion of leukotriene E4, a mast-cell product, after challenge with a bronchial allergen.

β2-Adrenergic receptors are present on both eosinophils and alveolar macrophages. The long-term administration of either salmeterol or formoterol decreases the concentration of eosinophilic cationic protein in bronchoalveolar-lavage fluid and serum, and salmeterol reduces the oxidative metabolism of alveolar macrophages. However, the numbers of activated lymphocytes in bronchoalveolar-lavage fluid or of eosinophils in blood and sputum do not change after long-acting β2-adrenergic agonists are administered for several weeks.

Despite their vascular and cellular effects, there is no evidence that β2-agonists have any substantial effect on the chronic inflammation characteristic of bronchial asthma. They should not be considered an alternative to inhaled corticosteroids as primary antiinflammatory therapy.

### Potential Adverse Reactions to β2-Adrenergic Agonists

Adverse reactions to β2-agonists can be divided into those that result from the expected pharmacologic actions of the drugs and those that could not be predicted from these properties.

#### Side Effects Due to Pharmacologic Actions of the Drugs

Because of the widespread distribution of β2-adrenergic receptors, a number of undesired responses result when β2-adrenergic bronchodilators are absorbed into the systemic circulation. The ability to avert these side effects by reducing plasma drug concentrations is one of the advantages of administering β2-adrenergic bronchodilators by inhalation.

The principal side effect of β2-adrenergic therapy is tremor, which is caused by the direct stimulation of β2-adrenergic receptors in skeletal muscle. Increased heart rate and palpitations are less common with the selective β2-agonists than with nonselective β1-β2-agonists such as isoproterenol. However, even stimulation of β2-adrenergic receptors can result in vasodilation and reflex tachycardia. Furthermore, some of the β2-adrenergic receptors in the atria and ventricles are β1 in type; thus, direct stimulation of the heart results from the use of even selective β2-agonists. Nevertheless, cardiac symptoms are rare in patients receiving customary doses of inhaled β2-agonists. In patients with acute, severe asthma, β2-adrenergic agonists may

### Table 2. Technique for Inhalation of β2-Adrenergic Agonists from Metered-Dose Inhalers.

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Shake the canister thoroughly.</td>
</tr>
<tr>
<td>2</td>
<td>Hold the mouthpiece of the inhaler 4 cm in front of the open mouth, or use spacer between the inhaler and the mouth.</td>
</tr>
<tr>
<td>3</td>
<td>Breathe out slowly and completely.</td>
</tr>
<tr>
<td>4</td>
<td>Discharge the inhaler while taking a slow, deep breath (5 to 6 seconds).</td>
</tr>
<tr>
<td>5</td>
<td>Hold the breath at full inspiration for 10 seconds.</td>
</tr>
</tbody>
</table>

*Based on information in Dolovich et al. and Hindle et al.*
cause a transient decrease in arterial oxygen tension, often of more than 5 mm Hg.46 The mechanism of this decrease is probably the relaxation of the compensatory vasoconstriction in areas of decreased ventilation,47 combined with increased pulmonary blood flow due to increased cardiac output. This is not a serious problem if the patient's oxygen saturation is monitored or if supplementary oxygen is administered.

Acute metabolic responses to β2-adrenergic agonists include hyperglycemia, hypokalemia, and hypomagnesemia. Because these responses diminish with regular administration,48 such changes are not important in patients receiving long-term therapy.

Side Effects That May Occur with Long-Term Administration

### Tolerance of β2-Adrenergic Agonists

A well-recognized effect of the regular administration of β2-adrenergic agonists is the development of tolerance (subsensitivity).13 Subsensitivity is readily demonstrated for the non-bronchodilator effects of the β2-agonists, including tremor, tachycardia, prolongation of the QTc interval on the electrocardiogram, hyperglycemia,49 hypokalemia,50 and the vasodilator response of blood vessels.50 Lessening of the bronchodilator response occurs in patients treated on a regular basis and results particularly in shortening of the duration of bronchodilation.51,52 The reduction develops over a period of weeks,51-53 and once established, the level is stable with continued use of the drug.55 Subsensitivity to the bronchodilator actions of the β2-adrenergic agonists also occurs in patients with chronic obstructive pulmonary disease54 and in those treated with the long-acting β2-agonist formoterol.55 Subsensitivity is presumed to be the clinical correlate of β2-adrenergic-receptor down-regulation. It may account for the decline in morning peak-expiratory-flow rates and forced expiratory volume in one second that is reported in patients who are not using sustained-release bronchodilators.56

Subsensitivity to the intermediate-duration β2-adrenergic agonists is of limited clinical importance. A reduction in the drugs’ duration of action is not crucial when they are used to relieve acute symptoms. The use of these drugs as maintenance bronchodilators is rarely appropriate now, since long-acting β2-adrenergic agonists have become available.

### Loss of Protection against Bronchoconstrictive Stimuli

β2-Adrenergic agonists shift to the right the dose-response curve of bronchial challenges with bronchoconstrictor stimuli including histamine, methacholine, AMP, exercise, and hyperventilation in dry, cold air; that is, more stimulus is needed to produce a given effect. With the long-term administration of both intermediate-acting51,52 and long-acting59,60 β2-adrenergic agonists, this protection was partially lost in some but not all studies.

AMP is thought to produce bronchoconstriction indirectly by releasing mediators from airway mast cells. The regular administration of a β2-adrenergic agonist resulted in a greater loss of protection against AMP-induced bronchoconstriction than against that induced by methacholine.58 This finding suggests that the β2-adrenoceptors on mast cells may be more susceptible to down-regulation than those on airway smooth-muscle cells.

It is likely that there is some loss of protection against other stimuli with long-term β2-adrenergic-agonist therapy. Exercise-induced bronchoconstriction is effectively blocked for 12 hours by the long-acting β2-adrenergic agonist salmeterol,61 but in one study this protection could no longer be demonstrated after four weeks of regular salmeterol therapy.62

The inhalation challenges often involve stimuli or large doses of an allergen that are not naturally encountered. Therefore, the partial loss of protection against these stimuli may not be clinically important.

### Bronchial Hyperresponsiveness

Discontinuation of regularly administered intermediate-acting β2-adrenergic agonists has been followed in some studies by increased bronchial responsiveness.63-65 The rebound increase in bronchial responsiveness is usually small as well as transient, and it is not likely to be clinically important. A transient increase in bronchial responsiveness has not been reported after the cessation of treatment with a long-acting β2-agonist.60

### Possible Mechanisms of the Adverse Effects of β2-Adrenergic Agonists

Theoretically, the regular administration of β2-adrenergic agonists could increase bronchial inflammation by blocking the antiinflammatory actions of mast cells or by allowing the inhalation of larger doses of allergen.66 On the basis of the results of experiments in guinea pigs, the dextro-enantiomer of β2-adrenergic bronchodilators could increase bronchial hyperresponsiveness.67

### Clinical Problems Associated with β2-Adrenergic Agonists

There have been sporadic reports of severe bronchospasm during or immediately after the inhalation of a β2-adrenergic agonist.68 Often these reactions are not reproducible and their cause cannot be determined. In at least some instances, they may result from an irritating effect of propellants69 at a time when the patient’s airways are particularly hyperresponsive. If the drug itself is responsible, the reaction will occur consistently and the patient will recognize the paradoxical response.70

In the 1960s, epidemics of increased mortality due to asthma occurred in six countries. Circumstantial evi-
idence linked the introduction of a metered-dose inhaler delivering a high dose of isoproterenol to this rise in mortality. In the 1970s, there was a second epidemic of deaths from asthma, this time limited to New Zealand. Again, epidemiologic evidence suggested that the epidemic was caused by fenoterol, a relatively non-selective \( \beta_2 \)-adrenergic bronchodilator, delivered at a higher dose than the other commonly used \( \beta_2 \)-adrenergic agonists. Three case-control studies of patients with asthma who died during this period indicated an increased risk of death among patients treated with fenoterol, and the risk increased further in subgroups selected for increased severity of asthma. Finally, a dramatic reduction in the use of fenoterol in New Zealand was temporally associated with a return of mortality due to asthma to low levels despite continued increases in total sales of \( \beta_2 \)-adrenergic agonists. Alternative explanations for the epidemics of deaths, such as underrecognition of the severity of asthma by both patients and physicians and underutilization of corticosteroid therapy, do not explain these abrupt and localized increases in mortality.

In an attempt to determine the relation of deaths due to asthma to the use of \( \beta_2 \)-adrenergic agonists, investigators examined the prescription of asthma medication and deaths and near-deaths in Saskatchewan, Canada. The results revealed that deaths increased among patients using more than 1.4 canisters of \( \beta_2 \)-agonist per month, and the greatest risk was associated with a pattern of increasing use. The investigators concluded that the greater use of \( \beta_2 \)-agonists was principally a marker of a greater severity of asthma, which itself was associated with an increased risk of fatal or near-fatal asthma.

**Overview of Therapy**

The value of the short-acting and intermediate-acting \( \beta_2 \)-adrenergic agonists, used as needed to relieve the symptoms of asthma, is accepted, as is their role in preventing exercise-induced asthma. In the emergency room, treatment of acute, severe asthma with these agents elicits the maximal attainable bronchodilation, with no further increase resulting from the addition of theophylline.

**Regular Use of \( \beta_2 \)-Adrenergic Agonists**

The use of \( \beta_2 \)-adrenergic bronchodilators on a regular basis is a matter of considerable controversy. In one study, asthma was better controlled (as assessed by a composite score that included peak airflow rates in the morning, symptoms, the need for corticosteroids, and bronchial hyperresponsiveness) when patients used only the \( \beta_2 \)-agonists of their choice as needed, as compared with regular use (four times daily) of fenoterol. The group that took fenoterol regularly also had exacerbations of asthma earlier and more often.

However, in double-blind studies of two weeks to three months of therapy with terbutaline and albuterol, the control of asthma was improved or at least did not deteriorate in patients who received regular treatment — as compared with “as needed” treatment — with the drugs. On balance, with the possible exception of fenoterol, regular (maintenance) therapy with \( \beta_2 \)-adrenergic agonists appears to have no adverse effects on patients with asthma.

**Long-Acting \( \beta_2 \)-Adrenergic Bronchodilators**

The newer, long-acting \( \beta_2 \)-adrenergic bronchodilators have overcome a major shortcoming of the previously available \( \beta_2 \)-adrenergic agonists: their relatively brief duration of action. With long-term therapy the action of short-acting drugs such as albuterol typically lasts only three to four hours. They are ill suited to provide protection during the night, when asthma symptoms are often worst. The effects of salmeterol and formoterol, on the other hand, may last up to 24 hours. Single doses of these drugs effectively block the response to exercise and cold air for at least 12 hours.

In placebo-controlled studies lasting three months, salmeterol in a dose of 50 \( \mu \)g twice daily significantly increased peak expiratory flow both when patients arose and in the evening, decreased asthma symptoms and the need for additional bronchodilator therapy, and decreased the frequency of nocturnal asthma. Similar results have been reported with formoterol. In one-year studies, the beneficial effect of salmeterol on pulmonary function was maintained. In prospective studies of patients treated for 3 to 12 months, there was no worsening of asthma, as measured by the occurrence of exacerbations or increased hospitalizations. In addition to improving airflow and decreasing symptoms, salmeterol, as compared with placebo, improved asthma-specific measures of the quality of life to a clinically important degree.

How should the new long-acting \( \beta_2 \)-adrenergic bronchodilators be used in patients with asthma? Current guidelines recommend that antiinflammatory therapy be initiated in patients who require frequent bronchodilator therapy. Therefore, antiinflammatory therapy should be introduced before a long-acting \( \beta_2 \)-agonist is given. A long-acting \( \beta_2 \)-agonist is not a substitute for antiinflammatory therapy; its use as needed to treat acute symptoms of asthma is not appropriate. When properly used, these drugs have not been associated with an unanticipated number of deaths due to asthma.

The long-acting \( \beta_2 \)-adrenergic agonists are properly administered as two inhalations twice daily to prevent symptoms of asthma. They are particularly effective for patients who awaken at night with asthma and for the prevention of exercise-induced asthma. For some patients who have only nocturnal awakening or exercise-induced symptoms, the long-acting \( \beta_2 \)-adrenergic agonists may be given once daily.

What about the patient who is already receiving low-dose inhaled corticosteroid therapy yet still has symptoms? This issue was addressed in a six-month study conducted in 99 general practices in England. Patients who remained symptomatic despite therapy with inhaled beclomethasone (200 \( \mu \)g twice daily) were treated with the same dose of beclomethasone plus sal-
meterol (50 μg twice daily), or the beclomethasone was increased to 500 μg twice daily. Symptoms of asthma, symptoms requiring additional bronchodilator agents, peak expiratory flow rates in the morning and the evening, and nocturnal awakening improved more in the combined-therapy group than in the group that received high-dose beclomethasone. The frequency of exacerbations of asthma was similar in the two groups. The results of this study suggest that adding a long-acting β₂-adrenergic agonist to corticosteroid therapy may be more appropriate for patients whose asthma is inadequately controlled by low-dose inhaled corticosteroids than increasing the dose of inhaled corticosteroids.

Special Considerations in the Clinical Use of β₂-Adrenergic Agonists

β₂-Adrenergic agonists are also used regularly for patients with chronic obstructive pulmonary disease. These patients’ response to anticholinergic drugs may or may not be greater than their response to β₂-adrenergic agonists. β₂-Adrenergic agonists do, nevertheless, improve airflow, functional exercise capacity, and the quality of life for patients with chronic obstructive pulmonary disease when these drugs are administered on a regular schedule.

The capacity of β₂-adrenergic agonists to produce bronchodilation in infants has been questioned because of the small amount of peribronchial smooth muscle. However, nebulized β₂-adrenergic agonists administered to 43 infants less than two years old who were brought to an emergency room with acute asthma were beneficial in the majority, as indicated by changes in clinical scores and oxygen saturation.

The safety of medication in pregnancy is always a source of concern, in regard to both possible teratogenesis and the effect on the course of the pregnancy. In a study of the perinatal outcomes of 259 women with asthma who were treated with inhaled β₂-adrenergic agonists during pregnancy, 101 pregnant women with asthma who were not treated with these drugs, and 295 pregnant women without asthma, there were no differences in the rates of perinatal mortality, congenital malformations, preterm delivery, or delivery of low-birth-weight infants, the mean birth weight, or the number of small-for-gestational-age infants. Nor were there differences in Apgar scores, rates of complications of labor or delivery, or postpartum bleeding. These results suggest that therapy with β₂-adrenergic agonists is safe in pregnant women.

Salmeterol is not currently approved for use in patients with chronic obstructive pulmonary disease or in children less than 12 years of age, and there is very limited experience with its use during pregnancy. For each patient, therefore, the potential beneficial effects of its use on the patient’s asthma must be balanced against the lack of experience with its use in these situations.

Conclusions

β₂-Adrenergic agonists are the most effective bronchodilators for the treatment of acute episodes of asthma and for the prevention of exercise-induced bronchoconstriction. The long-acting β₂-adrenergic agonists prevent nocturnal asthma and provide prolonged protection against exercise-induced bronchoconstriction. The long-acting β₂-adrenergic agonists should be administered only at regular, prescribed intervals. Additional doses should not be given to relieve symptoms; intermediate-acting β₂-agonists should be given instead. Despite some concern about these drugs as a class, the adverse effects are probably related more closely to the severity of the asthma than to the drug.

Thus, β₂-adrenergic agonists remain the most important class of bronchodilators currently available. When used appropriately, they provide safe and effective relief of the symptoms of airflow obstruction.

References

23. Nelson HS, Spector SL, Whitsett TL, George RB, Dwek JH. The broncho-
dilator response to inhalation of increasing doses of aerosolized albuterol.

24. Dolovich M, Ruffin RE, Roberts R, Newhouse MT. Optimal delivery of

25. Hindle M, Newton DAG, Chrystyn H. Investigations of an optimal inhaler
technique with the use of urinary salbutamol excretion as a measure of rel-

administered by metered dose inhaler (and holding chamber) or wet nebu-

27. Armstrong DL, Goldsmith WM, Hapason EF. Substitution of metered-dose in-
halers for hand-held nebulizers: success and cost savings in a large, acute-

28. Conner WT, Dolovich MB, Frame RA, Newhouse MT. Reliable salbuta-
monol administration in 6- to 36-month-old children by means of a measured
dose inhaler and Aerocachewith mask. Pediatr Pulmonol 1989;6:263-
7.

29. Davis B, Marin MG, Yee JW, Nadel JA. Effect of terbutaline on movement

30. Devalia JL, Sapsford RJ, Rusznak C, Toucham M, Davies RJ. The effects of
salmetrol and salbutamol on ciliary beat frequency of cultured human

31. Rhoden KJ, Meldrum LA, Barnes PJ. Inhibition of cholinergic neurotrans-
mission in human airways by b2-adrenoceptors. J Appl Physiol 1988;65:
700-5.

32. Breytaf I, Persson CG. Pharmacologic control of plasma exudation into tra-

33. Butchers PR, Vardey CJ, Johnson M. Salmeterol: a potent and long-acting
inhibitor of inflammatory mediator release from human lung. Br J Pharma-

34. O’Connor BJ, Fuller RW, Barnes PF. Nonbronchodilator effects of inhaled
b2 agonists: greater protection against adenosine monophosphate-
than methacholine-induced bronchoconstriction in asthma. Am J Respir


and late phase reaction to bronchial allergen and postchallenge vari-
tion in bronchial reactivity, blood eosinophils, serum eosinophil cationic

37. Wong BJ, Dolovich MB, Ramsdale EH, et al. Formoterol compared with bec-
olumethasone and placebo on allergen-induced asthmatic responses. Am Rev

38. Isawa T, Teshima T, Hirano T, et al. Does a b2-stimulator really facilitate mucociliary transport in

39. Mortensen J, Groth S, Lange P, Hermansen F. Effect of terbutaline on muc-
ciliary clearance in asthmatic and healthy subjects after inhalation from a

40. Taylor RI, Cheek KM, Choudry NB, Adachi M, Palmer JB, Fuller RW. A comparative study in atopic subjects with asthma of the effects of sal-

41. Gratziou C, Roberts JA, Walls A, Holgate ST, Howarth P. Lymphocytes pop-

42. Cockcroft DW, McParland C, Britton JA, Swystun VA, Rutherford BC. Reg-
ular inhaled salbutamol and airway responsiveness to allergen. Lancet 1993;
342:832-7.

43. O’Connor BJ, Aikman SL, Barnes PJ. Tolerance to the nonbronchodilator

44. Cheung D, Timmers MC, Zwinderman AH, Bel EH, Dijkman JH, Sterk PJ.
Long-term effects of a long-acting b2-adrenoceptor agonist, salmeterol, on

45. Booth H, Fishwick H, Karkawat R, Devereux G, Hendrick DJ, Walters EH.
Changes in methacholine induced bronchoconstriction with the long acting
beta 2 agonist salmeterol in mild to moderate asthmatic patients. Thorax 1993;

46. Kemp JD, Dockhorn RJ, Busse W, Bleecker ER, Van A As A. Prolonged ef-
fect of inhaled salmeterol against exercise-induced bronchospasm. Am J
Respir Crit Care Med 1994;150:1612-5.

47. Rasmage LG, Lithgow BJ, Ingram CR, Creg EA, Dhillon DP. Reduced protec-
tion against exercise induced bronchoconstriction after chronic dosing with

48. Wahedena I, Wong CS, Wisniewski AF, Paveord ID, Tattersfield AE. Asthma
control during and after cessation of regular beta 2-agonist treatment. Am

increase in bronchial responsiveness after treatment with inhaled terbutaline.

50. van Schaayck CP, Graafsma SJ, Visch MB, Dompeling E, van Weel C, van
Herwaerden CL. Increased bronchial responsiveness after inhaling salbuta-
olone during 1 year is not caused by desensitization to salbutamol. J Allergy

51. Page C. Asthma as a chronic inflammatory disease and the implications for

52. Morley J. Beta agonists and asthma mortality: deja vu? Clin Exp Allergy

53. Nicklas RA. Paradoxical bronchospasm associated with the use of inhaled

54. Wilkinson JR, Roberts JA, Bradding P, Holgate ST, Howarth PH. Paradoxi-
cal bronchoconstriction in asthmatic patients after salmeterol by metered

55. Finnerty JP, Howarth PH. Paradoxical bronchoconstriction with nebulized

56. Pearce N, Beasley R, Crane J, Burgess C, Jackson R. End of the New

57. Spitzer WO, Sussa S, Ernst P, et al. The use of b2-agonists and the risk of

asthma and the use of inhaled beta-agonists. Am J Respir Crit Care Med

59. Sussa S, Blais L, Ernst P. Patterns of increasing beta-agonist use and the

60. Sears MR, Taylor DR, Print CG, et al. Regular inhaled beta-agonist treat-
ment in bronchial asthma. Lancet 1990;336:1391-6.

61. Nelson HS, Szefer SJ, Martin RJ. Regular inhaled beta-adrenergic agonists
in the treatment of bronchial asthma: beneficial or detrimental? Am Rev

to optimal theophylline therapy: double blind crossover study in asthmatic

1992;327:1420-5.

64. D’Alonzo GE, Nathan RA, Hencowich S, Morris RJ, Ratner P, Remenn
SL. Salmeterol xinafoate as maintenance therapy compared with albuterol

Massachusetts Medical Society
Registry on Continuing Medical Education

To obtain information on continuing medical education courses in the New England area, call between 9 a.m. and noon, Monday through Friday, (617) 893-4610 or in Massachusetts 1-800-322-2303, ext. 1342.