Beta$_2$ Adrenergic Agents – Short-Acting Review

06/15/2009

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Beta$_2$ Adrenergic Agents, Short-Acting Review

FDA-Approved Indications

Drug Name	Manufacturer	Reversible Bronchospasm		Prevention of Exercise Induced Broncho-spasm	Chronic Obstructive Pulmonary Disease (COPD)	Age of Use (years)
		Prevention and Treatment	Relief			
Short-Acting Inhalation Agents						
albuterol HFA MDI (Proventil HFA, Ventolin HFA, ProAir HFA)[1,2,3]	Proventil HFA® Schering	X	X	X		≥4
	Ventolin HFA® GlaxoSmithKline					
	ProAir HFA® Ivax					
albuterol inhalation solution (Accuneb®)[4,5]	generic		X			2-12
levalbuterol inhalation solution (Xopenex®)[6]	Sepracor	X				≥6
levalbuterol HFA MDI (Xopenex® HFA)[7]	Sepracor	X				≥4
metaproterenol inhalation solution[8]	generic	X	X		X	≥6
pirbuterol MDI (Maxair® Autohaler)[9]	3M	X				≥12
Oral Agents						
albuterol oral syrup[10]	generic		X			≥2
albuterol oral tablets[11]	generic		X			≥6
metaproterenol oral syrup[12]	generic	X			X	≥6
metaproterenol oral tablets[13]	generic	X				≥6
terbutaline tablets[14]	generic		X		X	≥12

HFA=hydrofluroalkane; MDI=metered-dose inhaler

Overview

Beta$_2$-agonist bronchodilators are used for the treatment and prevention of bronchospasm associated with asthma, prophylaxis of exercise-induced bronchospasm (EIB), and in the treatment of chronic obstructive pulmonary disease (COPD).

Asthma

Short-acting beta$_2$-agonists have not been shown to be as beneficial as controller medications for asthma management, but due to their rapid onset, they are useful for temporary relief of bronchoconstriction and the accompanying acute symptoms such as wheezing, chest tightness, and cough.[15]

The 2007 guidelines from the National Heart Lung and Blood Institute recommend that for patients over age five years with moderate persistent asthma or asthma not controlled by low-dose corticosteroids that consideration be given for use of a combination of inhaled corticosteroids and long acting beta$_2$-agonists or for increasing the dose of inhaled corticosteroids. For patients with severe persistent asthma, a combination of a long acting beta$_2$-agonist and an inhaled corticosteroid is recommended. For exercise-induced bronchospasm, long acting beta$_2$-agonists may be used for prevention; however, it is noted that frequent or chronic use may disguise poorly controlled persistent asthma.

In November 2007, the National Asthma Education and Prevention Panel released a summary of the third report of the Expert Panel (EPR-3) that emphasizes the importance of asthma control and identifies asthma severity as the intrinsic intensity of the disease process. The recommendation from EPR-3 is to assess severity to initiate therapy and assess control to adjust therapy in patients as young as five years of age.

In 2007, the Global Initiative for Asthma (GINA) guidelines for asthma management were updated to reflect a change in focus from asthma severity to asthma control.[16] Asthma control is defined as no or minimal daytime symptoms; no limitations of activity; no nocturnal symptoms; no or minimal need for rescue medications; normal or near normal lung function; and no exacerbations. A five-step treatment approach is discussed in these guidelines that offer flexibility to step up treatment when asthma is uncontrolled or step down treatment when asthma is controlled. These guidelines suggest treatment with short-acting beta-$_2$ agonists only on an as-needed basis particularly if patients experience only occasional daytime symptoms of short duration. When symptoms are more frequent and/or worsen periodically, patients require regular controller therapy.

In 2008, the GINA guidelines were further updated to produce a more streamlined, user-friendly document that emphasizes the importance of asthma control with appropriate treatment. The asthma classification system is defined as three levels of control: controlled, partly controlled, or uncontrolled. Roles of other medications used to treat asthma (e.g. leukotriene modifiers, long acting beta-agonists, cromones and inhaled glucocorticoids) have evolved since prior versions of the guidelines and have been included in the 2008 update.[17]

COPD

Bronchodilator medications are central to the symptomatic management of COPD.[18,19,20,21] They improve emptying of the lungs, tend to reduce dynamic hyperinflation at rest and during exercise, and improve exercise performance. [22] They are given either on an as-needed basis for relief of persistent or worsening symptoms or on a regular basis to prevent or reduce symptoms. Regular bronchodilation with these drugs does not modify the decline of function in mild COPD or the prognosis of the disease.[23] The principal bronchodilator treatments are beta$_2$-agonists, anticholinergics, and theophylline. These may be given either as monotherapy or preferably, in combination with the inhaled agents. While short-acting beta$_2$-agonists can be used on an as-needed basis in mild COPD, regular treatment with a long acting agent is required as the disease progresses.[24]

In January 2008, the updated Global Initiative for chronic obstructive Lung Disease (GOLD) guidelines were released and state that beta$_2$-agonist bronchodilators are among the principal treatments for symptomatic management of COPD.[25] The guidelines also state that regular treatment with long-acting bronchodilators is more effective and convenient than treatment with short-acting bronchodilators.

In 2005, the American College of Chest Physicians (ACCP) and the American College of Allergy, Asthma, and Immunology (ACAAI) issued joint evidence-based guidelines for selecting aerosol delivery devices for use in asthma or COPD.[26] The authors performed a systematic review of randomized controlled trials comparing the efficacy and adverse effects of treatment using nebulizers versus pressurized MDIs with or without a spacer/holding chamber versus DPIs as delivery systems for beta$_2$-agonists, anticholinergic agents, and corticosteroids in several commonly encountered clinical settings and patient populations. The authors conclude that devices used for the delivery of bronchodilators and steroids can be equally efficacious.

Pharmacology

Beta-agonists stimulate adenyl cyclase, the enzyme that catalyzes the formation of cyclic-3'5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). Increased cyclic AMP levels are associated with relaxation of bronchial smooth muscle and inhibition of release of mediators of immediate hypersensitivity, especially from mast cells. Beta$_2$-agonists relieve reversible bronchospasm by relaxing the smooth muscles of the bronchioles in conditions associated with asthma, COPD, or bronchiectasis. Bronchodilation may additionally facilitate expectoration.

Although there are both beta$_1$ and beta$_2$ receptors in the heart, the latter are more predominant in the lungs, where they serve as the primary adrenergic receptors in bronchial smooth muscle. In order to reduce cardiac toxicities (e.g., tachyarrhythmias), the use of beta$_2$ specific agonists is preferred in the treatment of bronchospasm. This has minimized the use of less specific and less safe agents such as epinephrine (Primatene Mist®) and isoproterenol (Isuprel®). To further reduce cardiac toxicities, non-systemic dosage forms given by inhalation are preferred to oral dosage forms.

Since the signing of the Montreal Protocol in 1987, new propellants, such as hydrofluoroalkane (HFA), for use in pressurized metered-dose inhalers that are non-ozone-depleting have been developed. Several randomized, double-blind, placebo-controlled, crossover studies have shown that albuterol MDI pressurized by HFA are equivalent, in terms of efficacy and tolerability, to the original chlorofluorocarbon (CFC) albuterol MDI in both adolescents and adults.[27,28,29,30] This equivalence was shown for both the treatment and prophylactic (EIB) indications of albuterol. The reformulation effort is underway for the CFC containing products. The FDA completed its phase-out of albuterol inhalers using ozone-depleting CFCs as propellants on December 31, 2008. Patients who used albuterol inhalers containing CFCs were switched to alternative inhalers that contain a propellant called hydrofluoroalkane (HFA).

Pharmacokinetics

Drug	Relative ß$_2$ Specificity	Onset of Action (minutes)	Duration of Action (hours)
Short-Acting Inhalation Agents			
albuterol HFA MDI (ProAir HFA, Proventil HFA, Ventolin HFA)[31,32,33]	ß$_2$ >> ß$_1$	5.4-8.2	3-6
albuterol inhalation solution (generic, Accuneb)[34,35]	ß$_2$ >> ß$_1$	5-15	3-6
levalbuterol inhalation solution (Xopenex)[36]	ß$_2$ >> ß$_1$	10-17	5-8
levalbuterol HFA MDI (Xopenex HFA)[37]	ß$_2$ >> ß$_1$	5-10	3-6
metaproterenol inhalation solution[38]	ß$_2$ > ß$_1$	5-30	2-6
pirbuterol MDI (Maxair)[39]	ß$_2$ > ß$_1$	$\leq$ 5	5
Oral Agents			
albuterol syrup, tablets[40,41]	ß$_2$ >> ß$_1$	30	4-8
metaproterenol syrup, tablets[42]	ß$_2$ > ß$_1$	30	$\geq$4
terbutaline tablet[43]	ß$_2$ >> ß$_1$	30	4-8

Contraindications/Warnings[44,45,46,47,48,49,50,51,52]

No specific contraindications exist for the short-acting beta-agonists.

Warnings that are common to the short-acting beta-agonists include: paradoxical bronchospasm (can be life threatening), cardiovascular effects (e.g. effects on blood pressure and pulse rate), excessive dose and usage, acute deterioration of asthma and use of anti-inflammatory agents (e.g. corticosteroids). Short-acting beta-agonists should be used with caution in patients with heart disease, seizure disorder, diabetes and hyperthyroidism.

There have been rare reports of seizures in patients receiving terbutaline; seizures did not recur in these patients after the drug was discontinued.

Drug Interactions[53,54,55,56,57,58,59,60,61,62]

Monoamine Oxidase (MAO) Inhibitors and Tricyclic Antidepressants

All beta$_2$-agonists should be administered with extreme caution to patients being treated with MAO inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval because these agents may potentiate the action of adrenergic agonists on the cardiovascular system. Allow two weeks after discontinuation of MAO inhibitors before initiating therapy with agents in this category.

Beta-Adrenergic Receptor Blocking Agents

Beta-blockers not only block the pulmonary effect of beta-agonists but may also produce severe bronchospasm in patients with asthma or COPD. Therefore, patients with asthma or COPD should not normally be treated with beta-blockers. However, under certain circumstances, such as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of

beta-adrenergic blocking agents in patients with asthma or COPD. In this setting, cardioselective beta-blockers could be considered, although they should be administered with caution.

Diuretics

The ECG changes and/or hypokalemia that may result from the administration of non-potassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical significance of these effects is not known, caution is advised in the coadministration of beta-agonists with non-potassium-sparing diuretics. Concomitant treatment with xanthine derivatives, steroids, or diuretics may potentiate any hypokalemic effect of adrenergic agonists.

Digoxin

Mean decreases of 16 and 22 percent in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of recemic albuterol, respectively, to normal volunteers who had received digoxin for ten days. The clinical significance of these findings for patients with obstructive airway disease who are receiving albuterol and digoxin on a chronic basis is unclear; nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol and levalbuterol.

Adverse Effects

Drug	Headache	Nausea/ Vomiting	Nervousness	Palpitations	Tachycardia	Tremor
Short-Acting Inhalation Agents						
albuterol HFA MDI (Proventil HFA, Ventolin HFA, ProAir HFA)[63,64,65]	7-20	7 - 10	7	<3	<3 - 7	2-7
albuterol inhalation solution (generic, Accuneb)[66,67]	nr	1.7 and .9	reported	reported	nr	reported
levalbuterol inhalation solution (Xopenex)[68]	7.6 - 11.9	<2	2.8 - 9.6	reported	2.7 - 2.8	0 - 6.8
levalbuterol HFA MDI (Xopenex HFA)[69]	reported	10.5	reported	reported	reported	reported
metaproterenol inhalation solution[70]	3.3	7.7 - 14	14.1	<1	2.5 – 16.6	2.5 – 33
pirbuterol MDI (Maxair)[71]	1.3	1.3	4.5	1.3	1.3	1.3
Oral Agents						
albuterol syrup[72]	4	<1 - 2	9 - 15	<1	1 - 2	10
albuterol tablets[73]	7	2	20	5	5	20
metaproterenol syrup[74]	1.1	1.3	4.8	<1	6.1	1.6
metaproterenol tablets[75]	7	0.8 - 3.6	20.2	3.8	17.1	16.9
terbutaline tablets[76]	7.8 - 10	1.3 - 10	<5 - 31	≤23	1.3 - 3	<5 – 38

Adverse effects data are reported as a percentage. Adverse effects data are obtained from package inserts and are not meant to be comparative. nr = not reported.

Special Populations[77,78,79,80,81,82,83,84,85]

Pediatrics

Most of the short-acting beta-agonists have been studied in pediatric patients and shown to be safe and effective in adults and children as young as two years of age. Important to note is that the safety and effectiveness of pirbuterol (Maxair) in children has not been proven. There is insufficient clinical data to establish safety and efficacy of terbutaline sulfate therefore, it is not recommended for patients under the age of 12 years.

Pregnancy

There are no adequate and well-controlled studies of these agents in pregnant women. Terbutaline is Pregnancy Category B. All of the short-acting beta-agonists are Pregnancy Category C. They should only be used during pregnancy if the potential benefit justifies the potential risk.

Other considerations – renal, hepatic, race, etc.

These agents have not been studied in a geriatric population. Special caution should be observed when using these agents in elderly patients with coexisting conditions like impaired renal function and cardiovascular disease that could be adversely affected by this class of drug.

No dosage adjustments needed in the hepatically impaired patients who use albuterol, albuterol HFA, pirbuterol, and levalbuterol.

Exercise caution and monitor the renally impaired who use albuterol, albuterol HFA, pirbuterol, levalbuterol. No special monitoring or dosage adjustments are needed in the renally impaired patients who use metaproterenol.

Dosages

Drug	Usual Adult Dosage	Usual Pediatric Dose	Availability
Short-Acting Inhalation Agents			
albuterol HFA MDI (Proventil HFA, Ventolin HFA, ProAir HFA)[86,87,88]	2 inhalations every 4-6 hrs as needed Prevention of EIB: 2 inhalations 15-30 minutes prior to exercise	2 inhalations every 4-6 hrs as needed Prevention of EIB: 2 inhalations 15-30 minutes prior to exercise	90 mcg per actuation
albuterol inhalation solution (generic, Accuneb)[89,90]	2.5 mg every 6-8 hrs as needed	0.63-2.5 mg three to four times daily as needed	generic: 2.5 mg/3 mL, 5 mg/mL
			Accuneb or low-dose generic: 0.63 mg/3 mL, 1.25 mg/3 mL
levalbuterol inhalation solution (Xopenex)[91]	0.63-1.25 mg three times daily	0.31-0.63 mg three times daily	0.31 mg/3 mL, 0.63 mg/3 mL, 1.25 mg/3 mL
levalbuterol HFA MDI (Xopenex HFA)[92]	2 inhalations every 4-6 hrs as needed	2 inhalations every 4-6 hrs as needed	45 mcg per actuation
metaproterenol inhalation solution[93]	10-15 mg three to four times daily	5-10 mg three to four times daily	8 mg/2 mL, 5 mg/mL, 12 mg/2 mL,
pirbuterol MDI (Maxair)[94]	2 inhalations every 4-6 hrs. Not to exceed 12 inhalations per day.	--	200 mcg per actuation
Oral Agents			
albuterol oral syrup[95]	2-4 mg every 6-8 hrs	0.1-0.2 mg/kg every 8 hrs	2 mg/5 mL
albuterol oral tablets[96]	2-4 mg every 6-8 hrs	2 mg every 6-8 hrs	2 mg, 4 mg
metaproterenol oral syrup[97]	20 mg three to four times daily	10 mg three to four times daily	10 mg/5 mL
metaproterenol oral tablets[98]	20 mg three to four times daily	Age 6 – 9 yo or weight < 60lbs: 10 mg three to four times daily Age > 9yo or weight > 60lbs: 20 mg three to four times daily	10 mg, 20 mg
terbutaline tablets[99]	2.5-5 mg three times daily	2.5 mg three times daily	2.5 mg, 5 mg

Clinical Trials

Search Strategy

Articles were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the use of all drugs in this class. Randomized, controlled, comparative trials are considered the most relevant in this category. Studies included for analysis in the review were published in English, performed with human participants and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question and include follow-up (endpoint assessment) of at least 80 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

ASTHMA

albuterol MDI (Proventil, Ventolin) versus formoterol DPI (Foradil)

Formoterol DPI 12 mcg or 24 mcg twice daily was compared to albuterol MDI 180 mcg four times daily and placebo in a total of 541 patients with mild-to-moderate asthma in a twelve-week, multicenter, randomized, double-blind, parallel-group study.[100] At all measured time points during the 12 hours after the first dose, mean percentages of predicted FEV_1 values for formoterol and albuterol groups were significantly higher than those for the placebo group ($p \leq 0.037$). Formoterol, 12 mcg and 24 mcg were associated with a significantly higher percentage of predicted FEV_1 values than albuterol ($p \leq 0.018$ and $p \leq .00,1$ respectively) at hours four through six and at hour 12. The percentages of predicted FEV_1 values for albuterol were significantly greater than those for formoterol, 12 mg ($p \leq 0.027$) at five minutes through 60 minutes, and at hours seven and eight.

A study compared the efficacy and tolerability of formoterol DPI 12 mcg and 24 mcg twice daily with albuterol MDI 180 mcg four times daily and placebo.[101] A total of 554 adolescents and adults (ages 12-75 years) with mild to moderate asthma were randomized to the four treatment groups, of which 484 patients completed the 12-week, multicenter, double-blind, double-dummy, placebo-controlled, parallel-group study. For the primary efficacy variable, FEV_1, both formoterol DPI 12 and 24 mcg were statistically superior to placebo at all time points on all test days ($p \leq 0.017$) and to albuterol MDI at most time points on all test days ($p \leq 0.001$). The onset of improvement in FEV_1 was rapid with 15 percent increase within five minutes in 57, 71, and 65 percent of formoterol DPI 12 mcg, formoterol DPI 24 mcg, and albuterol MDI patients, respectively. Formoterol DPI was also showed greater improvement to placebo and albuterol MDI in terms of secondary efficacy variables: AUC, percentage of predicted FEV_1, forced vital capacity (FVC), asthma symptom scores, and peak expiratory flow rate (PEFR). Formoterol DPI and albuterol MDI were both well-tolerated.

Eighteen patients with EIB were randomized in a double-blind, placebo-controlled, four-way, crossover study.[102] Each patient received, in random sequence, a single dose of formoterol DPI 12 or 24 mcg, albuterol MDI 180 mcg, or placebo at intervals of three to seven days. Pulmonary function measurements were taken before and after exercise challenge tests at 15 minutes

postdose and at four, eight, and 12 hours postdose. Both doses of formoterol DPI produced significantly greater protection against EIB than placebo at all time points ($p \leq 0.016$). The two doses of formoterol DPI were not significantly different from one another at any time. Protection against EIB with albuterol MDI was clinically significant only at the 15 minute postdose time point and was statistically superior to placebo at 15 minutes and four hours. Rescue medication was used substantially less with either dose of formoterol DPI, compared with albuterol MDI or placebo. All treatments were well tolerated. Two-hour postdose electrocardiograms (ECGs) and vital signs were unremarkable for all study treatments.

In a double-dummy, four-way, crossover study, 20 adult and adolescent asthmatic patients received single doses of formoterol DPI 12 and 24 mcg, albuterol MDI 180 mcg, and placebo.[103] Exercise challenge tests were conducted at 15 minutes and at four, eight, and 12 hours postdose. Of the 20 patients who were enrolled, 17 patients completed the study. Compared with placebo, both doses of formoterol DPI produced significantly greater inhibition of FEV_1 decreases at all time points ($p<0.01$). There were no significant differences in efficacy measures between the two formoterol DPI doses throughout the study. The exercise-induced decrease in FEV_1 after albuterol MDI treatment was significantly reduced compared with placebo only at 15 minutes after dosing ($p<0.05$). Formoterol DPI and albuterol MDI exhibited a similar rapid onset of action (<15 minutes), but formoterol DPI continued to protect patients against EIB for at least 12 hours ($p<0.01$), whereas albuterol MDI was no longer clinically effective by the four hour exercise challenge test.

albuterol inhalation solution (Proventil, Ventolin) versus levalbuterol inhalation solution (Xopenex)

In a randomized, double-blind, placebo-controlled, crossover study, 20 adults with mild to moderate asthma received single doses of levalbuterol inhalation solution (0.31, 0.63, and 1.25 mg) and albuterol inhalation solution (2.5 mg).[104] All doses of active treatment produced a significantly greater degree of bronchodilation (measured by change in FEV_1) than placebo, and there were no significant differences between any of the active treatment arms. The bronchodilator response of levalbuterol 1.25 mg and albuterol 2.5 mg were clinically comparable over the six hour evaluation period, except for a slightly longer duration of action after administration of levalbuterol 1.25 mg. Systemic beta adrenergic adverse effects were observed with all active doses. Levalbuterol 1.25 mg produced a slightly higher rate of systemic beta adrenergic adverse effects than the albuterol 2.5 mg dose.

A multicenter, randomized, double-blind, placebo- and active-controlled study was conducted in 338 children with mild to moderate asthma.[105] Following a one week placebo run-in period, subjects were randomized to nebulized levalbuterol 0.31 or 0.63 mg, albuterol 1.25 or 2.5 mg, or placebo given three times daily for three weeks. Of the 338 patients who were randomized, 316 patients completed the study. Efficacy, measured by mean peak change in FEV_1, was demonstrated for all active treatment regimens compared with placebo. The onset and duration of effect of levalbuterol were clinically comparable to those of albuterol.

A randomized, double-blind, controlled trial was conducted in children age one to 18 years (n=482) in the emergency department (ED) and inpatient asthma care unit of an urban tertiary children's hospital.[106] Patients received a nebulized solution of either 2.5 mg racemic albuterol or 1.25 mg levalbuterol every 20 minutes (maximum six doses). Patients admitted to the asthma care unit were treated in a standardized fashion by using the same blinded drug assigned in the ED. Hospitalization rate was the primary outcome. Hospitalization rate was significantly lower in the levalbuterol group (36 percent) than in the racemic albuterol group (45

percent, p=0.02). The adjusted relative risk of admission in the racemic group compared with the levalbuterol group was 1.25 (95% confidence interval (CI), 1.01 - 1.57). Hospital length of stay was not significantly shorter in the levalbuterol group (levalbuterol, 44.9 hours; racemic albuterol, 50.3 hours; p=0.63). No significant adverse events occurred in either group.

COPD

albuterol MDI (Proventil, Ventolin) versus formoterol DPI (Foradil) versus salmeterol DPI (Serevent) in COPD

A cross-over, randomized, double-blind, placebo-controlled study was carried out on 20 COPD patients.[107] Patients underwent pulmonary function testing and dyspnea evaluation in basal condition and five, 15, 30, 60 and 120 minutes after bronchodilator (albuterol MDI, formoterol DPI, or salmeterol DPI) or placebo administration. The results indicated that in COPD patients with decreased baseline inspiratory capacity, there was a much greater increase of inspiratory capacity after bronchodilator administration, which correlated closely with the improvement of dyspnea sensation at rest. On average, formoterol DPI elicited the greatest increase in inspiratory capacity than the other bronchodilators used, though the difference was significant only with salmeterol DPI.

Meta Analyses

A systematic review of pertinent randomized, controlled, clinical trials was undertaken using MEDLINE, EmBase, and the Cochrane Library databases to determine if a difference in efficacy and adverse effects exists among the various aerosol delivery devices (MDI versus DPI versus nebulizers) used in the management of asthma and COPD exacerbations.[108] A total of 254 outcomes were tabulated. Of the 131 studies that met the eligibility criteria, only 59 (primarily those that tested beta$_2$-agonists) proved to have useable data. None of the pooled meta-analyses showed a significant difference among devices in any efficacy outcome in any patient group for each of the clinical settings that were investigated. The adverse effects that were reported were minimal and were related to the increased drug dose that was delivered. Each of the delivery devices provided similar outcomes in patients using the correct technique for inhalation.

Summary

Due to its rapid onset of action, relative lack of adverse systemic effects, and availability of multiple dosage forms, albuterol remains the most commonly used short-acting beta$_2$-agonist bronchodilator. Albuterol CFC MDIs are no longer available as of December 31, 2008. Schering (Proventil HFA), Ivax (ProAir HFA) and GlaxoSmithKline (Ventolin HFA) produce albuterol inhalers using HFA propellant.

In general, oral dosage forms of albuterol are less utilized than the inhaled forms due to systemic beta-adrenergic stimulation of the former, especially in patients sensitive to these effects, such as those with cardiovascular disease. Metaproterenol is neither as beta$_2$ selective nor as long acting as albuterol, therefore should not be considered for first-line therapy. Another beta$_2$-agonist, terbutaline, is more beta$_2$ selective than metaproterenol but is available only as oral tablets. The short duration of action of terbutaline reduces its value in the treatment of bronchoconstriction.

Levalbuterol (Xopenex) is the R-enantiomer form of albuterol. Levalbuterol (Xopenex)

inhalation solution has similar efficacy to albuterol inhalation solution when given in equivalent doses. In addition, an HFA-propelled inhaler containing the enantiomer of albuterol is available as levalbuterol HFA (Xopenex HFA). There are no significant differences in adverse effects between albuterol and levalbuterol formulations.

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