

Pharmacokinetics, pharmacodynamics, and the delivery of pediatric bronchodilator therapy

David P. Skoner, MD Pittsburgh, Pa

β_2 -adrenergic receptor agonists have long been used for the amelioration of acute asthma symptoms and in the prophylactic treatment of exercise-induced asthma in both adults and children. To maximize the amount of drug that reaches the airways, small doses of the drug can be inhaled in aerosol form that preferentially activate pulmonary β_2 -receptors, thereby reducing systemic absorption and adverse effects. Potential adverse effects of β_2 -agonists include tremor, increased heart rate, and metabolic imbalances. Because of its specialized nature, aerosolized delivery to the airways has many additional variables that can alter the pharmacokinetics and pharmacodynamics of the administered drug. (J Allergy Clin Immunol 2000;106:S158-64.)

Key words: Pediatric asthma, β_2 -agonists, pharmacokinetics, pharmacodynamics, drug delivery, metered dose inhaler, nebulizer, dry powder inhaler, spacers

METHODS OF DETERMINING DELIVERY AND DEPOSITION

After aerosolized drug delivery, airborne particles are deposited in the mouth, on the oropharynx, and in the airways. A large proportion of the drug is swallowed and then absorbed through the gastrointestinal mucosa to undergo first-pass metabolism in the liver. Absorption across the buccal mucosa is also possible. In fact, only about 20% of the aerosolized drug is delivered into an adult's airways. Various methods can minimize the oral and gastrointestinal absorption and increase the therapeutic ratio of drug that is delivered to the airways. In experimental settings, rinsing of the mouth and throat has reduced buccal absorption, and swallowing a charcoal suspension has reduced both gastrointestinal and buccal absorption. Although these techniques can limit the amount of drug absorbed systemically, blood levels still increase through the absorption of drug in the lungs.

Several methods can determine blood and lung levels of drug for pharmacokinetic analysis. In 1 method, concentrations in the blood can be assayed directly by the use of gas chromatography after inhalation. A problem with this procedure is the difficulty in measuring low levels of drug after delivery of microgram doses into the airways. To visualize and quantify deposition in the lungs

Abbreviations used

CFC: Chlorofluorocarbon

DPI: Dry powder inhaler

MDI: Metered-dose inhaler

and oropharynx, technetium Tc 99m-labeled drug in combination with a gamma camera can be used.

Urine concentrations of the drug and its sulfated metabolite may also be assayed as an indirect measure of systemically absorbed drug. This technique gives an indication of relative gastric mucosal and lung absorption because sulfate-conjugated products are generated primarily by drug that is absorbed across the gastrointestinal tract and buccal mucosa, whereas the unchanged drug represents the inhaled fraction absorbed through the lungs. For example, the urinary excretion of albuterol and its sulfated metabolite can be used to indicate the relative bioavailability of drug delivered to the lung after inhalation.¹

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES

Many β_2 -agonist formulations are currently used to treat asthma, including inhaled formulations, syrups, and extended-release tablets for decreasing the frequency of administration. This review will focus on drug administered through the inhaled route. There are 2 types of β_2 -agonists: short-acting, for quick relief; and long-acting, for prolonged control of symptoms. Albuterol (also known as salbutamol) is 1 of the most widely used inhaled β_2 -agonists for the treatment of asthma. It is a short-acting agent with a half-life of 4 to 6 hours. The time to maximum plasma concentration ranges from 0.5 hour for nebulized delivery to 2 to 4 hours for delivery by a metered-dose inhaler (MDI). The time to maximum clinical effect is approximately 1 hour with the inhaled drug and approximately 2 to 3 hours with the systemically delivered drug. Long-acting β_2 -agonists that are currently used to treat asthma include salmeterol and formoterol, the latter of which is not yet available in the United States. The half-life of salmeterol is approximately 5.5 hours. The time to maximum plasma concentration for the MDI route of administration for salmeterol consists of 2 values: the first peak occurs very early (within 5 minutes) and is most likely related to absorption across the pulmonary vascular bed, and a second peak occurs at 45 minutes, which reflects the drug absorbed from the gastrointestinal tract.

From the Children's Hospital of Pittsburgh.

Reprint requests: David P. Skoner, MD, Children's Hospital of Pittsburgh, 3705 Fifth Ave 4B320, Pittsburgh, PA 15213.

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β_2 -ADRENOCEPTOR POLYMORPHISM

The genetic polymorphism of the β_2 -adrenoceptor may play an important role in the response to β_2 -agonists. Nine polymorphisms in the β -adrenoceptor gene have been described. Some of these are associated with a reduced bronchodilator response to albuterol in both asthmatic and nonasthmatic children.² The asthmatic children with some of these variants are more likely to be steroid dependent. Consequently, these polymorphisms may underlie poor therapeutic responses to β_2 -agonist in patients with difficult-to-manage asthma.

EFFECT OF THE DISEASE STATE

The pharmacokinetics of inhaled β_2 -agonist can be influenced by the disease state. Compromised airway patency, a hallmark of asthma, results in unique pharmacokinetic characteristics of β_2 -agonist use. In normal adults, cumulative doses of 1 mg and 4 mg of inhaled albuterol were administered through an MDI; the doses were separated by 40 minutes. Albuterol plasma levels were monitored for 1 hour (Fig 1).³ Five minutes after inhalation of 1 mg of albuterol, plasma levels peaked at approximately 5 ng/mL. After a total cumulative inhalation of 4 mg, there was a rapid increase to peak plasma concentration within 5 minutes and then a slow reduction. The first 30 minutes likely represented absorption across the pulmonary vascular beds. In a similar study in adult asthmatic patients (mean percent predicted FEV₁, 56% $\pm$ 14%), these same investigators determined the pharmacokinetics of albuterol absorption across the compromised airway (Fig 2).⁴ The 1-mg cumulative dose produced a peak plasma concentration of albuterol (2 ng/mL) that was markedly lower than that seen with normal persons (5 ng/mL). After the 4-mg cumulative dose, there was a rapid, sustained rise in plasma levels, which suggests a prolonged release from the lung vascular bed into the circulation. The lower plasma albuterol concentrations in comparison to those obtained in normal individuals suggest that the compromised asthmatic airway decreased pulmonary deposition and absorption of β_2 -agonists. The time of maximum concentration in asthmatic patients appears to be close to 60 minutes; the more prolonged elimination, especially with the 4-mg dose, may reflect an altered clearance in asthmatic lungs.

EFFECT OF INHALATION TECHNIQUE

The effects of deep inhalation compared with buccal deposition were studied with the use of 8 puffs of albuterol that were administered over 5 minutes in symptom-free asthmatic adults.⁵ Albuterol (800 μ g) or placebo was delivered either during deep inhalation or after the deep inhalation. Heart rate was measured over a period of 30 minutes, and no change was detected with buccal administration of albuterol. When albuterol was deeply inhaled, however, heart rate was significantly increased (Fig 3). These results suggest that the changes

in heart rate result from systemic levels of drug absorbed through the pulmonary vascular bed, rather than through the buccal mucosa.

EFFECTS OF CARRIER PROPELLANT AND DELIVERY DEVICE

Different techniques used to deliver β_2 -adrenergic agonists into the airways are the MDI, the nebulizer, and the dry powder inhalers (DPIs). The DPI has potential disadvantages, including the need for adequate inspiratory flow rates and possible irritation of the airways by the powder itself.

The influence of the type of MDI inhalation device on the systemic absorption of albuterol was compared by the use of a standard MDI and a modified, low-velocity actuator device.³ Significantly higher plasma albuterol concentrations were observed with this modified device than with the standard MDI (Fig 4). With the standard MDI, there was an abrupt rise in albuterol levels, but a greater rise with the low-velocity actuator device was observed. This higher delivery and absorption translated into greater systemic effects, which was made evident by a shift to the left of several dose-response curves (Fig 5). There were a larger reduction in serum potassium levels and larger increases in heart rate and tremor at each dose with the low-velocity actuator device than with the MDI.

MDIs have generally used chlorofluorocarbon (CFC)-containing aerosols, but with the proposed worldwide ban of CFCs, nonchlorinated propellants must be explored. In addition to safety and efficacy questions that must be answered about the new non-CFC propellants, their potential influence on the pharmacokinetics of the drug must also be assessed.

The safety and efficacy of the non-CFC propellant HFA 134a versus the CFC propellant were compared in adult patients with asthma.⁶ After cumulative inhalations of albuterol at 30-minute intervals, no significant difference was observed in the change of FEV₁ for the 2 groups. No differences in heart rate, serum potassium levels, blood pressure, or adverse events were detected between the 2 groups, which indicated that HFA 134a was a safe and effective alternative propellant for the delivery of albuterol.

With the use of a cumulative dosing design, salmeterol was similarly studied in 12 healthy, nonasthmatic adults in a double-blind, randomized crossover study.⁷ Salmeterol was administered through an MDI every 60 minutes. Over a dose range from 50 to 200 μ g, no differences between CFC and non-CFC MDIs were observed for pulse rate, blood pressure, tremor, QT_c interval, or plasma glucose levels. At a dose of 400 μ g, however, the salmeterol/HFA 134a inhaler resulted in less of a decline of plasma potassium levels. The clinical relevance of this effect is debatable because of the high cumulative doses of salmeterol that produced this effect. It was concluded that the HFA 134a formulation did not change the pharmacodynamics of salmeterol.

The bioavailability to the lung of albuterol administered through a CFC-containing MDI, CFC-free MDI,

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FIG 1. Plasma albuterol after inhalation of a single dose in nonasthmatic adults. Cumulative doses of 1 mg and 4 mg of inhaled albuterol, separated after 40 minutes, were administered by way of MDIs. Five minutes after inhalation of 1 mg, plasma levels peaked around 5 ng/mL. After 4 mg, there was a rapid increase to peak plasma concentration within 5 minutes, followed by a slow reduction. (From Newnham DM, Wheeldon NM, Lipworth BJ, McDevitt DG. Single dosing comparison of the relative cardiac beta 1/beta 2 activity of inhaled fenoterol and salbutamol in normal subjects. *Thorax* 1993;48:656-8. With permission from the BMJ Publishing Group.)

FIG 2. Plasma albuterol after inhalation of a single dose in asthmatic adults. A 1-mg dose of inhaled albuterol produced a peak plasma concentration of 2 ng/mL, markedly lower than in normal persons. After a 4-mg dose, there was a rapid and sustained rise in plasma levels. (From Lipworth BJ, Newnham DM, Clark RA, Dhillon DP, Winter JH, McDevitt DG. Comparison of the relative airways and systemic potencies of inhaled fenoterol and salbutamol in asthmatic patients. *Thorax* 1995;50:54-61. With permission from the BMJ Publishing Group.)

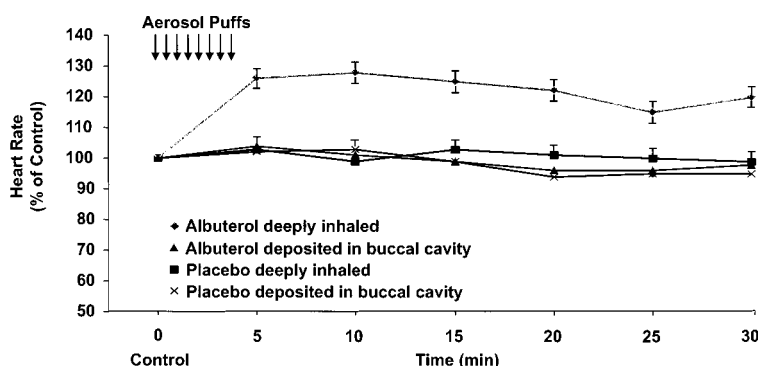


FIG 3. Comparison between deep inhalation and buccal deposition of albuterol. Heart rate was measured over a 30-minute period after 800 μ g of albuterol or placebo was delivered during or after deep inhalation. (From Collier JG, Dobbs RJ, Williams I. Salbutamol aerosol caused a tachycardia due to the inhaled rather than the swallowed fraction. *Br J Clin Pharmacol* 1980;9:273-4. With permission.)

and DPI were compared in healthy men (Table I).⁸ After albuterol (1200 μ g) had been inhaled, plasma levels were measured at 5, 10, and 20 minutes. These early measures reflect the pulmonary deposition of β_2 -agonist. At 5 and 20 minutes, there was a significantly higher level of plasma albuterol with the CFC-free formulation. No significant difference between the CFC and DPI formulations was observed. No changes in tremor or potassium levels for the 3 formulations were noted, which indicates no systemic effect of these 3 different delivery systems. These results suggest a higher pulmonary deposition and absorption with the CFC-free formulation than with the DPI or the CFC formulation of albuterol.

Increasing total doses of formoterol (12, 24, 48, and 96 μ g) were administered by either DPI or MDI with a

spacer to adult patients with moderate reversible asthma.⁹ No significant difference of the increase in FEV₁ was obtained with each device at each dose level, which indicates that both the DPI and MDI formulations of formoterol were equipotent in producing bronchodilation. The systemic effects on heart rate and tremor were obtained after each dose. At the higher doses (48 and 96 μ g), a slight but statistically significant increase in heart rate and tremor were detected with the DPI, which suggests that the DPI was delivering more drug systematically than did the MDI, perhaps through a combination of increased oral and/or lung deposition.

There is more than 1 device used to deliver dry powder β_2 -agonist. The systemic effects of albuterol, delivered by the Turbuhaler (AstraZeneca Pharmaceuticals, Wilming-

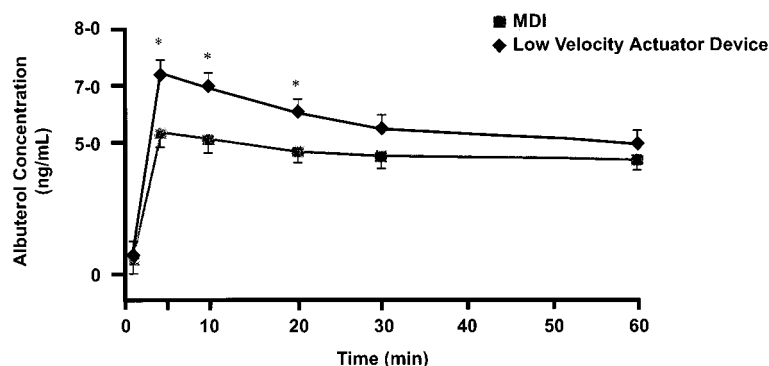


FIG 4. Influence of the inhalation device on the systemic absorption of albuterol. Significantly higher plasma albuterol concentrations were observed with a modified, low-velocity actuator device. (From Newnham DM, McDevitt DG, Lipworth BJ. Comparison of the extrapulmonary β_2 -adrenoceptor responses and pharmacokinetics of salbutamol given by standard metered-dose inhaler and modified actuator device. *Br J Clin Pharmacol* 1993;36:445-50. With permission.)

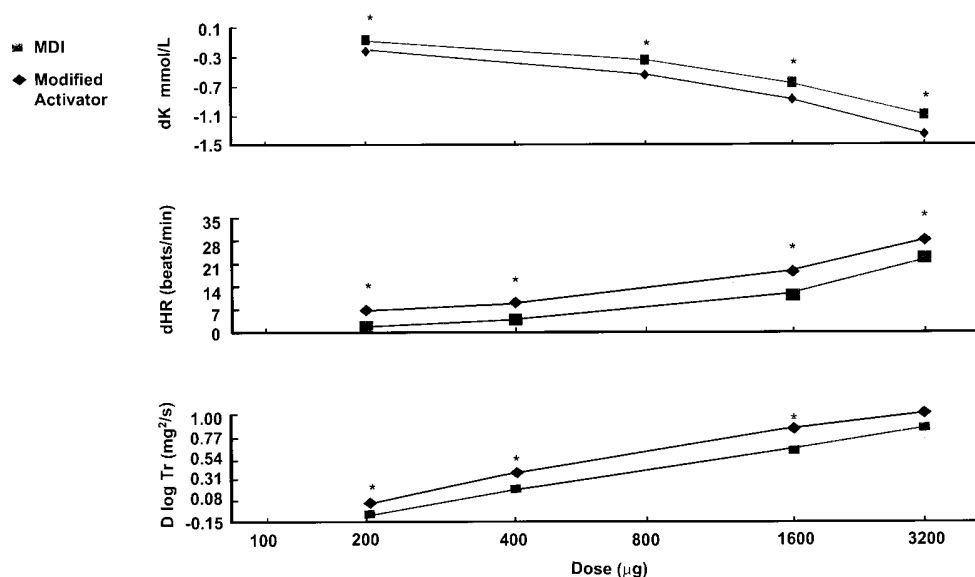


FIG 5. Systemic effects of a low velocity actuator device versus MDI. The higher delivery and absorption of the low velocity actuator device translated into greater systemic effects are made evident by a shift to the left of several dose-response curves. (From Newnham DM, McDevitt DG, Lipworth BJ. Comparison of the extrapulmonary β_2 -adrenoceptor responses and pharmacokinetics of salbutamol given by standard metered-dose inhaler and modified actuator device. *Br J Clin Pharmacol* 1993;36:445-50. With permission.)

ton, Del.) and Diskus (GlaxoWellcome, Research Triangle Park, N.C.), were compared in 8 healthy adult volunteers.¹⁰ Single doses of 1.2 mg albuterol as Turbuhaler or Diskus were administered over 6 minutes, followed by mouth rinsing after each dose to lessen the amount absorbed through the gastrointestinal tract. Plasma albuterol levels were measured at 5, 10, 15, and 20 minutes after inhalation as an indicator of lung deposition from each device. Significant differences were seen between the 2 inhalers, with the Turbuhaler producing a greater airway delivery than the Diskus (Fig 6). This increase in drug delivery also translated into significant changes in heart rate, with the Turbuhaler increasing heart rate more significantly than the Diskus.

USE OF SPACERS

Spacers have been shown to enhance airway drug delivery in those patients with poor MDI technique. Whether spacers differ in this capacity was tested in vitro with an examination of the delivery of 2 different drugs (albuterol and beclomethasone) with an MDI alone and with several different spacers (Table II).¹¹ There was no differential effect of the spacers on the amount of albuterol that reached the airways. With beclomethasone, however, some of the spacers compromised the amount of beclomethasone delivered. Therefore, spacers affect the delivery of drug into the lungs in a drug-specific fashion.

To directly assess the lung deposition patterns of drug

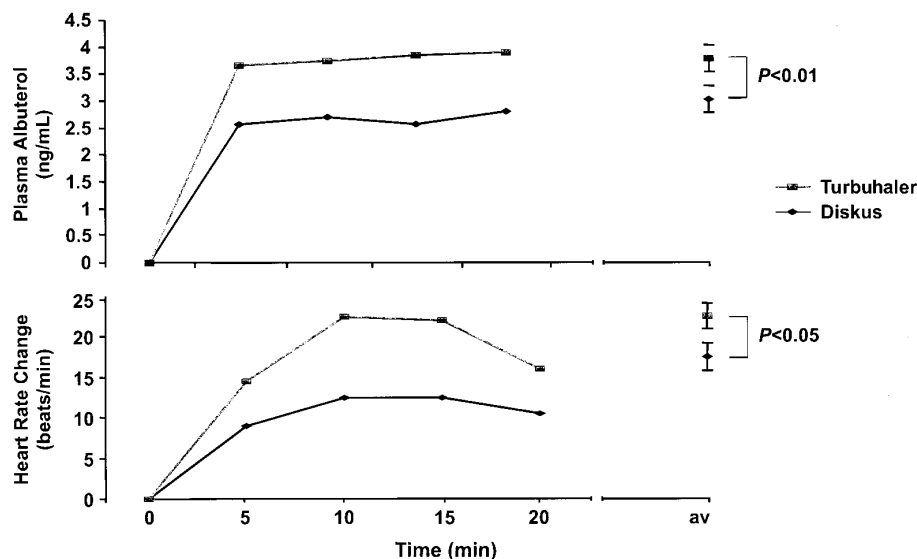


FIG 6. Comparison of systemic effects with 2 DPIs. Plasma albuterol levels were measured at 5, 10, 15, and 20 minutes after the inhalation of single doses of 1.2 mg albuterol over 6 minutes with the use of the Turbuhaler or Diskus. Significant differences were seen between the 2 inhalers, with the Turbuhaler producing a greater airway delivery than the Diskus. (From Lipworth BJ, Clark DJ. Comparative lung delivery of salbutamol given Turbuhaler and Diskus dry powder inhaler devices. *Eur J Clin Pharmacol* 1997;53:45-9. With permission.)

TABLE I. Mean plasma albuterol with CFC-containing MDI, DPI, and CFC-free MDI

Time of plasma albuterol (min)	CFC (ng/mL)	DPI (ng/mL)	CFC-free (ng/mL)
5	3.13*	3.14*	3.85
10	3.23	3.36	3.87
20	2.83*	3.13*	3.80

* $P < .05$, different than CFC-free.

From Clark DJ, Lipworth BJ. Lung bioavailability of chlorofluorocarbon free, dry powder and chlorofluorocarbon containing formulations of salbutamol. *Br J Clin Pharmacol* 1996;41:247-9. With permission.

after aerosol administration, albuterol should be directly labeled with ^{99m}Tc and quantified with a gamma camera.¹² In such a study, 10 healthy and 19 asthmatic adults inhaled 200 μg of albuterol using an MDI alone, an MDI with spacer, and a DPI, on separate days. Use of the DPI resulted in a lower delivery of albuterol than that of the MDI and the MDI with a spacer. Peripheral lung deposition with the MDI was much lower in patients with asthma than in persons without asthma, which illustrates the airway obstruction in asthmatic patients. Adding a spacer device significantly increased the amount of lung deposition in persons both with and without asthma when compared with the MDI alone.

The condition within the spacer and the choice of spacer itself also affect drug delivery and absorption. An electrostatic charge within plastic spacers was found to reduce the dose that reached the airways, with nonelectrostatic spacers permitting 2 to 4 times higher drug delivery to the airways.¹³ Likewise, cleaning the spacer with household detergent can reduce the electrostatic charge, permitting greater delivery (45.6% vs 11.5%).¹⁴

PEDIATRIC ASTHMA

The pediatric patient poses many unique challenges.¹⁵ Children younger than 5 years of age have small airways and, consequently, higher airway resistance. Additionally, their airways lack elastic recoil, thereby prolonging a period of bronchoconstriction. Collateral channels (Pores of Kohn), which decrease negative pressure in the airways, are deficient in both number and size. The horizontal position of the rib cage substantially increases the work of breathing and decreases efficiency because of the high negative pressures required to expand the thorax. The pediatric rib cage is also much less rigid, which leads to a higher degree of retraction. In addition, respiratory syncytial virus infection in children may induce wheezing that is clinically indistinguishable from asthma.

Nebulizer delivery in very young children is usually the first choice of treatment compared with the use of an MDI because of the difficult coordination between inhalation and activation of the MDI device. To compare the effectiveness of using an MDI and a spacer with that of a nebulizer, 3 puffs of albuterol (MDI and spacer; average age, 2.5 years) or standard nebulized treatment (average age, 2.1 years) were administered to children who came to the emergency department with an acute asthma exacerbation.¹⁶ In this acute, open-label study, the pulmonary function and outcomes (treatment time in the emergency department, episodes of vomiting, and increased heart rate) were measured. Both groups had the same improvement in pulmonary function in the emergency department, but the group using the MDI spent less time there (Table III). A greater incidence of vomiting and change of heart rate occurred in the nebulizer

TABLE II. Effects of spacer on amount of respirable drug

Drug dose (μg)	Drug and chamber	Amount reaching "respiratory" tract (μg ± SD)
90	Albuterol and MDI alone	35.72 ± 3.37
	Albuterol + Ace	36.05 ± 1.82
	Albuterol + OptiHaler (Respironics, Pittsburgh, Pa.)	35.45 ± 1.27
	Albuterol MDI + AeroChamber (Forest, St. Louis, Mo.)	34.50 ± 3.79
	Albuterol MDI + InspirEase (Schering-Plough, Kenilworth, N.J.)	40.65 ± 5.02
42	Beclomethasone and MDI alone (Schering-Plough, Kenilworth, N.J.)	21.62 ± 1.40
	Beclomethasone + Ace (DHD, Canastota, N.Y.)	4.43 ± 0.67
	Beclomethasone + OptiHaler	9.70 ± 0.69
	Beclomethasone + AeroChamber	6.98 ± 1.01
	Beclomethasone + InspirEase	13.94 ± 1.05

From Ahrens R, Lux C, Bahl T, Han SH. Choosing the metered-dose inhaler spacer or holding chamber that matches the patient's need: evidence that the specific drug being delivered is an important consideration. *J Allergy Clin Immunol* 1995;96:288-94. With permission.

TABLE III. MDI plus a spacer versus nebulizer in pediatric asthma

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TABLE IV. Effect of age on drug absorbed in lungs

Measure	Age		P-value
	≤5 y	>5 y	
Administered dose of salbutamol (μg/L)	181.3	131.9	.059
Prenebulizer plasma salbutamol concentration (μg/L)	9.2	27.0	.011
Postnebulizer plasma concentration (μg/L)	13.1	30.9	.011
Absolute change in salbutamol concentrations (μg/L)	4.0	3.9	.926
Percentage change in plasma salbutamol concentration	64.7	16.6	.002
Fraction of administered dose apparently absorbed	0.075	0.162	.010

From Penna AC, Dawson KP, Manglick P, Tam J. Systemic absorption of salbutamol following nebulizer delivery in acute asthma. *Acta Pediatr* 1993;82:963-6. With permission.

group than in the MDI-with-spacer group, which suggests greater systemic bioavailability with a nebulizer. Therefore, MDIs with spacers are an effective alternative to nebulizers for the treatment of children with acute asthma exacerbations in the emergency department because they provide good lung delivery with lower systemic bioavailability.

The doses of β_2 -agonist delivered with the use of an MDI with spacer and face mask for infants and small children are not yet well defined. Moreover, the risk of administering high doses of drug to small children is still unknown. To ascertain the effect of age on the amount of albuterol absorbed from the lungs, a study was undertaken in 35 children on the morning after hospital admission for acute asthma.¹⁷ Children were divided into 2 groups: 5 years of age or younger and older than 5 years of age. Plasma albuterol levels were measured on admission and after nebulizer therapy. The prenebulizer plasma levels were higher in children older than 5 years of age than in children 5 years of age or younger (Table IV). Postnebu-

lizer plasma levels were also lower in children 5 years of age or younger when compared with the older group. Based on the calculated fraction of administered dose absorbed, even though the younger children had a relatively higher dose administered, they absorbed a lower fraction of this dose than did the older children. The results of this study suggested that very young children may require higher relative doses because of possible problems in nebulizer technique or differences in pharmacokinetics (higher clearance).

A separate study that determined the deposition of inhaled drug in very young asthmatic children used ^{99m}Tc-labeled albuterol that was delivered from an MDI through a spacer with mask.¹⁸ The deposition in the oropharynx, lungs, stomach, and spacer mask was measured with a gamma camera immediately after 1 puff of labeled albuterol. Children ranged in age from 3 months to 5 years (mean age, 21 months). Using this device, children were able to achieve a deposition of almost 2% in the lung, 1.3% in the oropharynx, and 1.1% in the stomach;

the remainder stayed in the spacer. In 2 adult volunteers who used a mouthpiece instead of a face mask, a 19% deposition in the lungs was achieved. This study might suggest that higher doses of albuterol should be used in smaller children to achieve optimal results (or benefit).

The standard albuterol solution is a racemic mixture of the 2 enantiomers, (S)-albuterol and (R)-albuterol (levalbuterol). Levalbuterol produces bronchodilation, whereas (S)-albuterol is pharmacologically inactive but is thought to be responsible for some of the unwanted side effects of racemic albuterol. The safety and efficacy of nebulized levalbuterol in children with asthma was recently addressed in a dose-ranging study.¹⁹ This single-dose, randomized, double-blind, crossover study examined children (3 to 11 years) who were treated with levalbuterol (0.31 and 0.63 mg), racemic albuterol (1.25 and 2.5 mg), or placebo. The lowest dose of levalbuterol produced a greater improvement in FEV₁ over 8 hours than did the highest dose of the racemic mixture. Moreover, the high dose of the racemic mixture resulted in more systemic side effects, including greater changes in heart rate and serum potassium levels, than did the low dose of levalbuterol.

CONCLUSIONS

The use of inhaled β_2 -agonist in the amelioration of the symptoms of asthma presents unique challenges in achieving the delivery of drug to the site of action. This is especially true for children in whom a minimal systemic absorption is desirable to limit the adverse effects of β_2 -agonists. The issue in children is further complicated by the variability of the inhaled dose absorbed, which can depend on the age of the child. It has been shown that many factors, in addition to the choice of drug itself, have an impact on the pharmacokinetics and pharmacodynamics of bronchodilator therapy when inhaled agents are used. The choice of delivery device (MDI or DPI) and the formulations themselves (racemic mixtures, CFC vs non-CFC propellant) can alter the amount of drug that reaches the airways and is systemically absorbed and the efficacy and the side effect profile of the β_2 -agonist.

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