

Comparing Clinical Features of the Nebulizer, Metered-Dose Inhaler, and Dry Powder Inhaler

David E Geller MD

Introduction
Drug/Device Combinations
Device Advantages and Disadvantages
Clinical Evidence
Errors With Aerosol Devices
Making a Choice: Young Children
Adult Example
Decisions, Decisions
Summary

Topically inhaled bronchodilators and corticosteroids are the mainstay of treatment for asthma and chronic obstructive pulmonary disease. These medications are delivered via jet or ultrasonic nebulizer, metered-dose inhaler (MDI), or dry powder inhaler (DPI). While the number of devices may be confusing to patients and clinicians, each device has distinct advantages and disadvantages. Most clinical evidence shows that any of these devices will work for most situations, including exacerbations and in the stable outpatient setting. There is a high rate of errors in device use with all these devices, especially the MDI. In choosing a drug/device combination for a patient, the clinician must take into account several factors, including the cognitive and physical ability of the patient, ease of use, convenience, costs, and patient preferences. Clinicians should also have a rudimentary understanding of aerosol principles in order to be able to teach appropriate use of aerosol devices to their patients. *Key words: aerosol, asthma, bronchodilator, corticosteroids, chronic obstructive pulmonary disease, COPD, dry powder inhaler, DPI, metered-dose inhaler, MDI, nebulizer, drug delivery.* [Respir Care 2005;50(10):1313–1321. © 2005 Daedalus Enterprises]

Introduction

Topical application of drugs to the lung via inhalation is a technique that is centuries old. The history of aerosol-

David E Geller MD is affiliated with The Nemours Children's Clinic, Orlando, Florida.

David E Geller MD presented a version of this article at the 36th RESPIRATORY CARE Journal Conference, Metered-Dose Inhalers and Dry Powder Inhalers in Aerosol Therapy, held April 29 through May 1, 2005, in Los Cabos, Mexico.

Correspondence: David E Geller MD, The Nemours Children's Clinic, 83 W Columbia Street, Orlando FL 32806. E-mail: dgeller@nemours.org.

device development was reviewed by Anderson at these proceedings,¹ and by Rau in a recent review paper.² Others at these proceedings have extensively reviewed the principles of design and operation of the metered-dose inhaler (MDI) and dry powder inhaler (DPI). This discussion will focus on the clinical features of aerosol devices and how caregivers decide which aerosol delivery system is appropriate for their patients.

The increasing number of inhaler devices and device types can be very confusing to patients and caregivers alike, and it can be very frustrating to choose inhaler devices for an individual patient. Many of the inhaled drugs may be marketed in one or two of the inhaler systems but not all three. There are advantages and disadvantages of

COMPARING CLINICAL FEATURES OF THE NEBULIZER, MDI, AND DPI

Table 1. Bronchodilator Devices Available in the United States

	Nebulizer	MDI	Breath-Actuated	DPI Single-Dose	DPI Multi-Dose
Albuterol	Yes	Yes*	No	No	No
Levalbuterol	Yes	Yes*	No	No	No
Pirbuterol	No	No	Yes	No	No
Ipratropium	Yes	Yes	No	No	No
Albuterol + ipratropium	Yes	Yes	No	No	No
Salmeterol	No	No	No	No	Yes
Formoterol	No	No	No	Yes	No
Tiotropium	No	No	No	Yes	No

*Available in hydrofluoroalkane formulation

Table 2. Inhaled Corticosteroid Devices Available in the United States

	Nebulizer	MDI	Breath-Actuated	DPI Single-Dose	DPI Multi-Dose
Beclomethasone	No	Yes*	No	No	No
Budesonide	Yes	No	No	No	Yes
Budesonide/formoterol	No	Yes†	No	No	No
Ciclesonide	No	Yes†	No	No	No
Flunisolide	No	Yes†	No	No	No
Fluticasone	No	Yes*	No	No	No
Fluticasone/salmeterol	No	Yes†	No	No	Yes
Mometasone	No	No	No	No	Yes
Triamcinolone	No	Yes	No	No	No

*Available in hydrofluoroalkane formulation
 †Future launch as hydrofluoroalkane formulation

each type of aerosol device for various patient populations and clinical settings. Literally hundreds of papers have been published that compare inhalation devices and the drugs they deliver, and the authors' conclusions often differ. In the absence of clear-cut advantages for one device (or therapy) over another, there is often a fanaticism that develops among specialists, with pharmaceutical and device companies strongly favoring one drug/device combination over the others. However, when dealing with an individual patient we must ignore the banter and choose what will work best in the home, office, or hospital, according to numerous interactive variables. A review of devices will be presented, and examples of how our choices can be influenced by the patient will follow.

Once a device is chosen for a patient, the patient must be able to use it appropriately to ensure adequate lung delivery and maximize benefit from the drug. Proper use of most current devices is not intuitive and requires education and re-education of the patient.³ However, we know that in addition to patients, physicians, nurses, pharmacists, and respiratory therapists make several errors in the operation of these devices. Therefore, not only must the clinician be careful to select devices that patients are ca-

pable of using, but also those devices for which they can provide instruction. To ensure the best compliance with therapy, patients need to understand how the devices work and what the drugs actually do. If an inhaled therapy doesn't seem to be working for an individual, issues of compliance, belief systems, and understanding of their prescribed regimen should be reviewed before changing therapy.⁴

Drug/Device Combinations

In the optimal setting, the clinician would be able to choose the desired drug in any of the device types to fit the patient's needs. Internationally, there are more drug/device combinations available, but choices are limited in the United States. For example, in the United States there are no DPI formulations of short-acting β_2 agonists. Most are available in either nebulizer or MDI, and only one formulation (pirbuterol) is available in a breath-actuated device (Table 1). Conversely none of the long-acting bronchodilators are available in the United States in MDI form. Table 2 summarizes the inhaled corticosteroids available in the United States. Budesonide is available in all formats

internationally, but in the United States the MDI form is not available.⁵ With the exception of the newcomer mometasone (DPI), most of the other inhaled corticosteroids are available in MDI only. The combination formulation of fluticasone and salmeterol comes only as a DPI currently, but is being developed as an MDI. The finite choices of drug/device combinations may limit the clinician's ability to choose what he or she feels would be the best regimen, and it increases the likelihood that patients may be offered more than one type of device to control their asthma or chronic obstructive pulmonary disease (COPD). For example, the prescribed controller medication may be an inhaled corticosteroid/long-acting β_2 agonist DPI product, and the rescue medication an MDI. Since the inhalation techniques are different for the various devices, this may lead to increased confusion in the patient who uses more than one device type.

Device Advantages and Disadvantages

Each inhaler type has pros and cons that must be considered in the selection of a device for a particular patient.⁶ For example, there is no special technique for using jet nebulizers, as they are fairly intuitive to use and tidal breathing is sufficient. Nebulizers can be used at any age, and for any disease severity or acuity. In some cases it is possible to mix more than one medication in a nebulizer and deliver them simultaneously, though this lengthens the administration time. One of the benefits of nebulizers with diseases other than asthma and COPD is the ability to use very high drug doses. For example, inhalable tobramycin is a topical antibiotic for *Pseudomonas* endobronchial infections in cystic fibrosis. It comes as a unit dose of 300 mg, which would be impossible to deliver with an MDI. Most current DPIs also deliver very low doses of medication, but newer technology is allowing delivery of higher payloads of medication to the lung (eg, tobramycin inhalation powder).⁷ One of the subjective benefits of a nebulizer is that it seems to foster confidence in the patient (or parent) because it generates visible mist for several minutes, thereby assuring the patient that he or she is getting medication. There are no objective data to support that notion.⁸ Finally, nebulizers contain no propellants that can damage the atmosphere and they require very little teaching in clinic.

There are several disadvantages to nebulizers as well. Nebulizers are more time-consuming than either an MDI or DPI. Jet nebulizers require a source of compressed air, and they require equipment maintenance and cleaning for infection control. The classic nebulizer/compressor system is also less portable than an MDI or DPI, but newer, small, battery-operated devices are now available. Nebulizers are "open" devices that can aerosolize a number of drugs. The performance efficiency of different nebulizers is highly

variable and depends on numerous factors (eg, driving gas flow, fill volume, drug).⁹ Therefore, the amount of drug available for lung deposition is not predictable unless that particular device has been studied with the drug of interest. Ultrasonic nebulizers have historically been too expensive to consider for asthma and COPD treatment, but they are starting to become cheaper and more portable. Some of them produce a larger particle size distribution and they do not nebulize suspensions, such as budesonide, very well.¹⁰

The pressurized MDI has numerous advantages. It is small, portable, and can be used very quickly. Because of these features, it is the preferred device for asthma and COPD therapy in many countries. In many cases the MDI medication is less expensive, and some of the newer hydrofluoroalkane solutions have a very high lung deposition fraction ($\geq 50\%$). Because of the portability and the cost savings, some institutions in the United States are developing protocols to replace nebulizer therapy with MDI-with-holding-chamber treatments.¹¹

There are many problems with MDIs that must be considered. MDIs do not have incorporated dose counters, so it is difficult to tell how much drug remains. The technique and coordination required for efficient MDI use make it the most difficult of all the aerosol devices. If there is a delay between actuation and inhalation, or if the patient inhales too rapidly, the delivery to the lower airways will be affected. A whole industry of spacer and holding-chamber devices has popped up over the last 2 decades to help improve coordination and reduce the oropharyngeal deposition of the high-velocity sprays from MDIs. For the purposes of this discussion, the term "chamber" will be used to describe both spacers and holding chambers with valves. Adding a chamber to an MDI makes it less portable. If multiple actuations are put into a chamber at the same time, the delivery efficiency is reduced. Many chambers can develop static electrical charge on the inner walls, which attracts and attaches aerosol particles to the walls and thereby reduces the lung delivery, though washing the chamber in soapy water can reduce the static charge.^{12,13} The NebuChamber is a metal chamber that suffers less static charge, but is only available in Europe. Two new antistatic chambers are now available in the United States: the Vortex (Pari Respiratory Equipment, Midlothian, Virginia) and the AeroChamber Max (Trudell Medical International, Plattsburgh, New York).

Children under 4 years of age use chambers with face masks. The mask must fit tightly to the face, since the child must be able to open the valve of the chamber to allow medication to pass through. Since MDIs are the most difficult device to use, teaching MDI use may be a problem in a busy clinical practice. Also, even if patients understand perfectly how to use the device properly, they may contrive to use the devices incorrectly, thus not obtaining the maximum benefit. Brennan et al described a

group of asthma patients who knew that chambers should be used for inhaled corticosteroids, but contrived not to use them.^{14,15} With young children, the parent had the child open his or her mouth and shot the medication into the oropharynx. Only by asking patients exactly how they used their devices at home, and enacting a specific education program in clinic to combat poor technique, were they able to significantly lower the rate of chamber disuse from 76% to 11%.³ Clearly, the most education is required for proper use of MDI devices, and it would be helpful for the caregivers to learn some aerosol principles in order to teach devices correctly.

DPIs are the newest type of aerosol delivery device and come in many forms. There are single-dose devices that use drug contained in a capsule, multi-dose devices with bulk drug and a dosing chamber, and multi-dose devices with individual doses inside. In general, DPIs are easier to use than MDIs because they are breath-actuated. The energy from the patient's inhalation deaggregates the powder into smaller particles. DPIs do not contain propellants, and DPIs are very portable and quick to use. Spacers are not necessary with DPIs. The multi-dose DPIs incorporate dose counters and are easier to teach than MDIs.

Since a higher inspiratory flow is necessary to operate a DPI, some patients will be unable to use DPIs, especially very young children. DPIs are generally recommended for patients ≥ 5 years old and who have both adequate inspiratory flow and the cognitive ability to use the device appropriately. Adequate lung volume is also necessary to inhale the drug into the lower airways. It is generally thought that DPIs should not be used with patients who have low levels of lung function; however, Borgstrom has shown that in several clinical situations viewed as constrained, patients are still capable of generating enough flow to operate a DPI effectively, including patients with COPD, acute asthma, and children with asthma.¹⁶

Clinical Evidence

There is considerable literature arguing the merits of one delivery system versus another. In the June 2000 American Association for Respiratory Care sponsored consensus conference on aerosols and delivery devices there were 3 statements made that helped fuel the controversy:

1. "Because the MDI and DPI delivery systems are the most convenient and provide the lowest cost dose, they should be the first choice of clinicians."¹⁷

2. "MDI and DPI systems are underutilized in the United States in the acute care setting. Barriers to increased use of these devices should be identified. . . ."¹⁷

3. "Respiratory therapists can also implement protocols to increase the conversion of nebulizers to MDI and DPI delivery systems and to reduce the misallocation of aerosol therapy."¹⁷

These statements were predicated on a number of studies that showed equivalence of aerosol systems in the emergency department and hospital, the lower cost of MDIs and DPIs, and the availability of a short-acting β_2 agonists via DPI at the time (now off the United States market). Since short-acting β_2 agonists via DPI will probably never be developed for the United States market again (too expensive), and in light of new literature and other considerations, it is time to reevaluate the hard-line position against nebulizers.

Recent meta-analyses regarding the selection of aerosol delivery systems for acute asthma conclude that short-acting β_2 agonists delivered via either nebulizer or MDI/chamber are essentially equivalent.^{18,19} The literature is also clogged with numerous aerosol-device studies that were underpowered, biased, or poorly designed.

In a comprehensive effort that took several years, Dolovich et al reviewed this literature and published evidence-based guidelines for selection of aerosol devices.⁶ They looked for studies involving nebulizers, MDIs (with and without chambers), and DPIs for β_2 agonists, anticholinergic agents, and inhaled corticosteroids. They also reviewed literature on a variety of clinical settings (emergency department, inpatient, intensive care, and outpatient) and different patient populations (pediatric and adult asthma, and COPD). Only randomized controlled trials in which the same drug was delivered via different devices were included in the review. A total of 394 papers published between 1982 to 2001 were screened, out of which 131 studies met eligibility criteria. Of those, only 59 papers had data that could be utilized. A total of 254 different outcome variables were found and were categorized into 10 major groups. Of the 59 studies, 28 examined MDI versus DPI, 19 examined nebulizer versus MDI/chamber, 5 examined MDI versus MDI/chamber, and 4 examined DPI versus MDI/chamber. The vast majority of the studies involved short-acting β_2 agonists. None of the pooled analyses of these papers showed a significant difference between devices in any of the outcome variables or in any of the patient groups studied.⁶

In the acute emergency department setting, 19 studies with short-acting β_2 agonists were reviewed, 3 of which used DPIs (not available in the United States). Eight of these were pediatric studies that showed no difference in symptom scores or pulmonary function measures between nebulizer and MDI/chamber. Six adult studies likewise showed no difference in pulmonary function improvement, time spent in the emergency department, or the hospital admission rate between these 2 devices. There were 3 studies of DPI with adults, which also showed no difference in outcomes. The only consistent difference noted that there was greater increase in heart rate in the nebulizer group than in the MDI group, but that difference was small in magnitude.⁶

In the inpatient setting there were 6 studies of children and adults, which showed no difference in lung-function improvement or length of hospital stay between nebulizer and MDI/chamber. There was also conflicting evidence about the cost savings of the devices, with no conclusions drawn. In 3 studies of mechanically ventilated subjects, short-acting β_2 agonists worked equally well, whether delivered via MDI or nebulizer, as long as appropriate attention was given to the delivery technique to assure adequate lung deposition. In all of the emergency department and inpatient settings, patients received multiple doses of short-acting β_2 agonists over a period of time. Thus, all patients (regardless of delivery device) probably reached the plateau of the dose response curve.⁶

For outpatient asthma there were 28 studies of short-acting β_2 agonists reviewed. Most of the studies examined the acute response of pulmonary function to a single dose of drug. Twenty-three of the studies examined DPI versus MDI and showed no difference in pulmonary-function response (4 were pediatric studies). There is no relevance in the United States for short-acting β_2 agonists in DPI form, though these studies demonstrated the ability of children to use a DPI device. Some of the outpatient studies used dose-ranging techniques to show that it takes between 4 and 10 puffs of an MDI bronchodilator to equal a single nebulizer treatment.^{20–22} No outpatient asthma studies compared nebulized bronchodilator with other devices. There were 4 studies of inhaled corticosteroids in outpatient asthmatics. These studies showed that inhaled corticosteroids delivered via DPI or MDI/chamber to adults did not differ in symptom scores or pulmonary function over a few weeks' time. However, more patients preferred the DPIs. Finally, for outpatient COPD, 7 studies found that bronchodilator via nebulizer, MDI, or MDI/chamber is essentially equivalent.⁶

The bottom line of the Dolovich et al review is that each of the aerosol devices can work equally well in a variety of clinical settings in patients who can use these devices appropriately.⁶ This emphasizes the need for specific training in appropriate technique for use of these aerosol devices to achieve the clinical effect. The studies reviewed by Dolovich et al used different nebulizers, different MDI chambers, different DPI types, and different drugs (tantamount to comparing apples and oranges of different species!). The amount of drug delivered to the lungs depends not only on the general type of device used but also on the characteristics of the specific brand of device, which makes this review of the literature so remarkable. Newer studies have not contradicted the findings of this review for either short-acting β_2 agonists²³ or inhaled corticosteroids.²⁴

A recent meta-analysis of short-acting β_2 agonists in acutely wheezing children less than 5 years of age was recently reported.²⁵ Six randomized controlled trials were included in the analysis, spanning the years 1966 to 2003,

with a total of 491 subjects. The authors concluded that short-acting β_2 agonists delivered via MDI/chamber was more effective than via nebulizer for decreasing the hospital admission rate from the emergency department and improving symptom score. While this differs from the meta-analysis for older children and adults, there are potentially confounding variables in the younger children. For example, Rubilar et al studied 123 infants and toddlers with a mean age of 8 months, using either albuterol via MDI/chamber (2 puffs every 10 minutes for 5 treatments) or nebulized treatment every 20 min for 3 treatments.²⁶ Clinical success judged by improvement in clinical score was greater in the MDI group than in the nebulizer group for the first hour of treatment. However, it was noted by the authors that most of the infants cried when the face mask was applied. Since lung delivery decreases dramatically during crying, the children who had treatment via MDI/chamber would have received very little bronchodilator to the lower airways. Also, the efficacy of short-acting β_2 agonists in young infants with acute wheezing episodes is still very controversial. Therefore, it may not have been the short-acting β_2 agonists that led to the clinical improvement; rather, crying and mobilization of mucus from peripheral airways may have helped the clinical scores in the MDI/chamber group. Despite the shortcomings of this study, the other short-term pediatric studies in the emergency department were consistent with this one in showing more improvement with short-acting β_2 agonists via MDI/chamber.²⁵ The question remains, can we extrapolate this to chronic outpatient use?

Errors With Aerosol Devices

In most clinical trials, patients are coached and instructed on how to use the devices correctly. Patients who are incapable of using the devices are not included in the studies. This ideal doesn't exist in a typical outpatient setting. In many cases, patients given a prescription for an inhaler device may not have any instruction on inhaler technique other than a package insert. Several investigators have reported poor knowledge of inhaler technique among caregivers and patients. In the largest study of patient inhaler technique, Molimard et al described over 3,800 outpatients treated for at least one month with their prescribed inhalation devices.²⁷ They were observed and scored by their primary care practitioner for proper handling of the devices. Approximately half of the subjects made at least one error when using the Aerolizer, Autohaler, Diskus, or Turbuhaler. A greater proportion (76%) made at least one error with an MDI. Critical errors that would result in almost no medication reaching the lungs were made by 11–12% of patients using Aerolizer, Autohaler, and Diskus; 28% using MDI; and 32% using Turbuhaler. In a different study, almost half the subjects made

at least one error using a Handihaler device on a follow-up visit after initial training.²⁸

Nebulizer technique has been less well studied. One study found that only 18% of patients had “relevant” errors when using a nebulizer, but “relevant” was not well defined in the article.²⁹ Interestingly, 24% of the patients did not clean the nebulizer at all, which should negatively impact the performance of the device. Most of the patients who did clean their nebulizers were not disinfecting them appropriately.

Another study looked at MDI technique in a group of children recovering from acute asthma in the emergency department.³⁰ All of these children used an MDI at home, either with or without a chamber. Upon evaluation, about 45% of the children made multiple errors with either MDI alone or with chamber. Only 25% of the patients made no errors. Finally, studies show that most patients prescribed MDI do not know how many actuations there are per canister and do not know how to determine when the MDI is empty.³¹ All of these studies highlight the difficulties in using inhaler devices, but especially the MDI. So, even though the evidence shows clinical equivalence of the MDI, MDI/chamber, DPI, and nebulizer devices, the error rate among outpatients is the highest in the MDI group. Until we have adequate educational tools in place for teaching proper device techniques, the position favoring MDIs over nebulizers for all patients will be difficult to support.

Making a Choice: Young Children

Let us explore the logic of making a device choice for an infant or toddler with recurrent wheezing or asthma. We know that if a child cries during the administration of an aerosol, most of the inhaled drug is deposited in the throat and then swallowed. A substantial decrease in lung dose occurs if the child fusses or cries.³² One line of logic would be to use an MDI and chamber with mask to reduce the time that the mask is on the face of the young child, thus reducing the chances that the child might cry. This, in fact, is the logic employed in some countries and centers that exclusively use the MDI/chamber for administration of asthma medications to young children. However, when using a chamber with mask, the patient interface with the device is extremely important. Small leaks between the mask and face can significantly decrease the delivered dose.³³ The Netherlands group recently reported the results of a study that used a nose-throat model of a 9-month-old child (the Sophia Anatomical Infant Nose-Throat [SAINT] model) to study the effect of mask leak with an MDI/chamber. They simulated the breathing pattern of a 9-month-old and showed that even with very small leaks ($< 0.5 \text{ cm}^2$) there was a dramatic drop in lung dose with this model.³⁴

Avoiding mask leaks depends on the design of the mask and how well it fits the face, and on the cooperation of the child. Since at least a third of infants and toddlers will fuss during aerosol administration, it was thought that administering the MDI with chamber and face mask during sleep might avoid mask leak and improve aerosol delivery. The same investigators recorded breathing patterns from 18 infants while awake and asleep. They played these breathing patterns back using the SAINT model while delivering a puff of budesonide with a chamber and face mask. They noted that the lung dose in the SAINT model was doubled when using the sleeping respiratory pattern versus the awake pattern.³⁵ Therefore, one would expect that treating children while asleep would be more successful, based on this model. However, being careful investigators, they tested this theory with real infants between the ages of 6 and 23 months. Each child was given a dose of budesonide with a chamber and face mask while awake and while asleep. The dosing occurred over several days, and the results were averaged. What the investigators found was quite astonishing. In a reversal of the bench model, the inhaled dose was almost 3 times greater in the awake children than in the sleeping children.³⁶ About 69% of the children awakened when the mask was applied to the face and three fourths of those became very distressed, disrupting the mask fit and decreasing aerosol delivery. These data suggest that the majority of children cannot be treated with MDI/chamber while asleep.

These data seem very discouraging. How can we possibly treat these young children effectively with aerosols? Would nebulizer treatments be any better? Nebulizer treatments take longer, so there is a greater chance that the child will become fussy and cry, especially with a tight-fitting mask. To avoid making the child cry, many caregivers and parents use the blow-by technique, in which the aerosol is directed towards the child's nose and mouth (instead of applying a mask), but we have been taught for over a decade that blow-by technique is ineffective. In 1992, Everard et al used a bench model to study the inhaled dose with blow-by technique, with nebulizer and face mask.³⁷ The model was a simple, 35-mL open cylinder with a rim at the front, to which a face mask was applied. When the face mask was held away from the model only 2 cm, there was an 85% reduction in the inhaled dose—a great argument against blow-by technique. However, since the model was too simple, a new study recreated Everard's bench work to more carefully simulate the upper airway and breathing patterns of an infant. In the first study, tidal volumes ranging from 50 mL to 200 mL were used with a nose-breathing model. The inhaled dose from blow-by using a corrugated tube (up to 4 cm away from the model “nose”) was similar to that of a tight-fitting mask.³⁸ The corrugated tube concentrates the aerosol, which can be aimed toward the mouth or nose of the

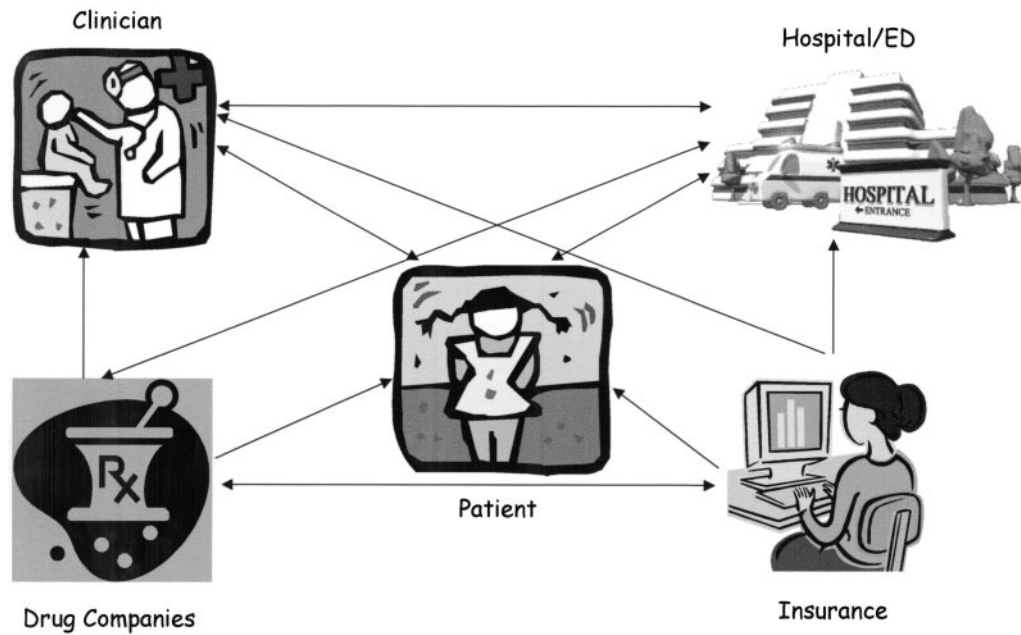


Fig. 1. Interactions that guide the choice of aerosol device.

infant model. In a follow-up study, the SAINT nose-throat model was used, and it validated prior results by showing that the lung dose was essentially equivalent between blow-by with a corrugated tube and a close fitting face mask.³⁹ It is conceivable that blow-by nebulizer treatment to a sleeping child could succeed, since it would not be necessary for a mask to touch the face. Others have shown that lung deposition using an aerosol hood with infants is similar to that of a nebulizer with a close-fitting face mask.⁴⁰ Though blow-by and hood therapy should be validated by clinical studies, anecdotal evidence exists from thousands of parents and respiratory therapists who swear by this technique to avoid the wrath of a screaming child.

A recent study with young children compared outcomes between those prescribed inhaled corticosteroids via nebulizer versus MDI/chamber.⁴¹ A large managed-care organization database was used to identify children ≤ 8 years old who had an emergency department visit or hospitalization with a primary diagnosis of asthma (index event). Patients prescribed an inhaled corticosteroid delivered either via nebulizer or via MDI/chamber were then followed for 6 months after the index event, to study the rate of recurrence of emergency care for asthma. The relative risk of emergency care for asthma in the nebulizer group was 29% lower than that of the MDI group.⁴¹ Whether this outcome was due to better aerosol technique or compliance is not known. However, these real-life data show the benefit of nebulizers for the longer term, versus the short-term emergency-department data that favor the MDI/chamber.

This pediatric example should not be construed as an argument for or against a particular aerosol device. Rather, I would argue that there is evidence that both nebulizers and MDI/chambers can work well with children, but with an individual patient we must be flexible and make choices based on many variables, especially the child's reaction to the treatment.

Adult Example

The need for versatility also exists in the adult population, especially with elderly patients. Let us take the case of a retiree on a fixed income who has moderate COPD. His physician prescribes fluticasone-salmeterol (Diskus) and tiotropium (Handihaler), as well as an MDI for albuterol. The cost of those therapies for the patient may be thousands of dollars a year, so he decides to forego one or more of the medications. Medicare Part B does not pay for DPIs or MDIs yet, but will cover 80% of the cost of a compressor nebulizer and nebulized drugs. Therefore, with that patient it may be preferable to treat with nebulized medications, solely on the basis of reimbursement and cost (and therefore compliance in this example). This situation may change in the future, with the implementation of the Part D drug benefit for Medicare in 2006.¹¹

Decisions, Decisions

There is a complex relationship between hospitals, insurers, pharmaceutical companies, caregivers, and patients,

with each influencing the other in many ways (Fig. 1). Choosing a drug/device combination can be the culmination of many variables, but the bottom line is delivery of the drug to the lower airway, and there are many ways of accomplishing that goal. Just as FedEx and UPS can both deliver a package from one place to another, so can different aerosol devices deliver drug particles to the lung.

In making the choice of aerosol drug/device combinations for an individual patient, we can ask the following questions:

1. Which devices are available that deliver the desired drug?
2. Is the device appropriate for the age and capability of the patient?
3. Is it covered by a third-party payer?
4. What are the costs to the patient? To society?
5. Is the drug/device combination approved by the Food and Drug Administration?
6. Can the same type of device be used for all inhaled drugs prescribed for an individual patient? (This would simplify the learning and teaching process.)
7. Which devices are the most convenient, inexpensive, portable, and time-saving in each clinical situation?
8. Which devices are the clinicians capable of teaching properly?
9. Which devices do the patient and/or parent prefer?

Summary

It is evident that patients need better education to properly use their inhalation devices. It is also evident that caregivers do not always understand the principles of how the devices operate and how to properly teach them. It will be important to educate clinicians in the elementary principles of aerosol delivery to the lung, so that they understand the do's and don't's of proper inhalation technique. The pharmaceutical and device industry should also be challenged to make devices that are more intuitive to use, to improve reliability of dosing, and to improve patient compliance. Regulatory agencies should be challenged to recognize the difficulties experienced with current devices and to offer guidance to industry to improve on the status quo. The principle of keep it simple definitely applies to the clinical use of aerosol devices. The devices should be simple and intuitive to use, and the clinicians should keep the treatment regimens as simple as possible while maintaining control over the airway disease.

ACKNOWLEDGMENTS

Many thanks to Bert Kesser for constructing the tables and reviewing the manuscript, and to Lisa Gregory for her help in the preparation of the manuscript.

REFERENCES

1. Anderson PJ. History of aerosol therapy: liquid nebulization to MDIs to DPis. *Respir Care* 2005;50(9):1139–1149.
2. Rau JL. The inhalation of drugs: advantages and problems. *Respir Care* 2005;50(3):367–382.
3. Everard ML. Inhaler devices in infants and children: challenges and solutions. *J Aerosol Med* 2004;17(2):186–195.
4. Rubin BK. What does it mean when a patient says, "My asthma medication is not working?" *Chest* 2004;126(3):972–981.
5. Thorsson L, Geller D. Factors guiding the choice of delivery device for inhaled corticosteroids in the long-term management of stable asthma and COPD: focus on budesonide. *Respir Med* 2005;99(7):836–849.
6. Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. *Chest* 2005;127(1):335–371.
7. Geller DE, Howenstine M, Conrad C, Smith J, Mulye S, Shrewsbury SB. A Phase I study to assess the tolerability of a novel tobramycin powder for inhalation (TPI) formulation in cystic fibrosis subjects (abstract). *Pediatr Pulmonol Suppl* 2004;27:250.
8. Poole PJ, Saini R, Brodie SM, Black PN. Comparison of the effects of nebulised and inhaled salbutamol on breathlessness in severe COPD. *Respir Med* 2005;99(3):372–376.
9. Rau JL. Design principles of liquid nebulization devices currently in use. *Respir Care* 2002;47(11):1257–1275.
10. Nikander K, Turpeinen M, Wollmer P. The conventional ultrasonic nebulizer proved inefficient in nebulizing a suspension. *J Aerosol Med* 1999;12(2):47–53.
11. Hendeles L, Hatton RC, Coons TJ, Carlson L. Automatic replacement of albuterol nebulizer therapy by metered-dose inhaler and valved holding chamber. *Am J Health Syst Pharm* 2005;15:62(10):1053–1061.
12. Wildhaber JH, Devadason SG, Eber E, Hayden MJ, Everard ML, Summers QA, LeSouef PN. Effect of electrostatic charge, flow, delay and multiple actuations on the in vitro delivery of salbutamol from different small volume spacers for infants. *Thorax* 1996;51(10):985–988.
13. Barry PW, O'Callaghan C. The effect of delay, multiple actuations and spacer static charge on the in vitro delivery of budesonide from the Nebuhaler. *Br J Clin Pharmacol* 1995;40(1):76–78.
14. Brennan VK, Osman LM, Graham H, Critchlow A, Everard ML. True device compliance: the need to consider both competence and contrivance. *Respir Med* 2005;99(1):97–102.
15. Brennan V, Everard ML. Contrivance: a major cause for failure of aerosol therapy in children. *Eur Respir J* 2002;20:429s.
16. Borgstrom L. On the use of dry powder inhalers in situations perceived as constrained. *J Aerosol Med* 2001;14(3):281–287.
17. Dolovich MA, MacIntyre NR, Anderson PJ, Camargo CA Jr, Chew N, Cole CH, et al. Consensus statement: aerosols and delivery devices. *American Association for Respiratory Care. Respir Care* 2000;45(6):589–596. Erratum in: *Respir Care* 2000;45(11):1416.
18. Cates C. Spacers and nebulisers for the delivery of β -agonists in non-life-threatening acute asthma. *Respir Med* 2003;97(7):762–769.
19. Cates CC, Bara A, Crilly JA, Rowe BH. Holding chambers versus nebulisers for β -agonist treatment of acute asthma. *Cochrane Database Syst Rev* 2003;(3):CD000052.
20. Pedersen JZ, Bundgaard A. Comparative efficacy of different methods of nebulising terbutaline. *Eur J Clin Pharmacol* 1983;25(6):739–742.
21. Madsen EB, Bundgaard A, Hiding KG. Cumulative dose-response study comparing terbutaline pressurized aerosol administered via a pearshaped spacer and terbutaline in a nebulized solution. *Eur J Clin Pharmacol* 1982;23(1):27–30.

22. Blake KV, Hoppe M, Harman E, Hendeles L. Relative amount of albuterol delivered to lung receptors from a metered-dose inhaler and nebulizer solution: bioassay by histamine bronchoprovocation. *Chest* 1992;101(2):309–315.
23. Deerojanawong J, Manuyakorn W, Prapphal N, Harnruthakorn C, Sritippayawan S, Samransamruajkit R. Randomized controlled trial of salbutamol aerosol therapy via metered dose inhaler-spacer vs. jet nebulizer in young children with wheezing. *Pediatr Pulmonol* 2005; 39(5):466–472.
24. Bisca N, Cernatescu I, Dragomir D, Iacomi A, Mirceau M, Orascanu D. Comparison of the efficacy and safety of beclometasone dipropionate suspension for nebulization and beclometasone dipropionate via a metered-dose inhaler in paediatric patients with moderate to severe exacerbation of asthma. *Respir Med* 2003;97 Suppl B:S15–S20.
25. Castro-Rodriguez JA, Rodrigo GJ. β -agonists through metered-dose inhaler with valved holding chamber versus nebulizer for acute exacerbation of wheezing or asthma in children under 5 years of age: a systematic review with meta-analysis. *J Pediatr* 2004;145(2):172–177.
26. Rubilar L, Castro-Rodriguez JA, Girardi G. Randomized trial of salbutamol via metered-dose inhaler with spacer versus nebulizer for acute wheezing in children less than 2 years of age. *Pediatr Pulmonol* 2000;29(4):264–269.
27. Molimard M, Raheison C, Lignot S, Depont F, Abouelfath A, Moore N. Assessment of handling of inhaler devices in real life: an observational study in 3811 patients in primary care. *J Aerosol Med* 2003;16(3):249–254.
28. Dahl R, Backer V, Oilgaard B, Gerken F, Kesten S. Assessment of patient performance of the HandiHaler compared with the metered dose inhaler four weeks after instruction. *Respir Med* 2003;97(10): 1126–1133.
29. Kofman C, Berlinski A, Zaragoza S, Teper A. Aerosol therapy for pediatric outpatients. *RT: J Respir Care Pract* 2004;117:26–28.
30. Scarfone RJ, Capraro GA, Zorc JJ, Zhao H. Demonstrated use of metered-dose inhalers and peak flow meters by children and adolescents with acute asthma exacerbations. *Arch Pediatr Adolesc Med* 2002;156(4):378–383.
31. Rubin BK, Durotoye L. How do patients determine that their metered-dose inhaler is empty? *Chest* 2004;126(4):1134–1137.
32. Everard ML. Trying to deliver aerosols to upset children is a thankless task (letter). *Arch Dis Child* 2000;82(5):428.
33. Amirav I, Newhouse MT. Aerosol therapy with valved holding chambers in young children: importance of the facemask seal. *Pediatrics* 2001;108(2):389–394.
34. Esposito-Festen JE, Ates B, van Vliet FJ, Verbraak AF, de Jongste JC, Tiddens HA. Effect of a facemask leak on aerosol delivery from a pMDI-spacer system. *J Aerosol Med* 2004;17(1):1–6.
35. Janssens HM, van der Wiel EC, Verbraak AF, de Jongste JC, Merkus PJ, Tiddens HA. Aerosol therapy and the fighting toddler: is administration during sleep an alternative? *J Aerosol Med* 2003;16(4):395–400.
36. Esposito-Festen JE, Ijsselstijn H, Hop WCJ, van Vliet FJ, de Jongste JC, Tiddens HA. Aerosol therapy by pMDI-spacer in sleeping young children. To do or not to do? (abstract) *J Aerosol Med* 2005;18(1): 109.
37. Everard ML, Clark AR, Milner AD. Drug delivery from jet nebulisers. *Arch Dis Child* 1992;67(5):586–591.
38. Geller DE, Kesser B. Blowby vs. face mask for nebulized drugs in young children (abstract). *J Allergy Clin Immunol* 2004;113(2):S32.
39. Kesser KC, Geller DE. Blowby nebulization revisited (abstract). *J Aerosol Med* 2005;18(1):105.
40. Amirav I, Balanov I, Gorenberg M, Groshar D, Luder AS. Nebuliser hood compared to mask in wheezy infants: aerosol therapy without tears! *Arch Dis Child* 2003;88(8):719–723.
41. Camargo CA Jr, Patel P, McLaughlin T, Leibman C. Budesonide inhalation suspension (BIS) reduces risk of recurrent emergency department (ED) visits or hospitalizations in asthmatic children (abstract). *Am J Respir Crit Care Med* 2004;169(7 Suppl):A286.

Discussion

Smaldone: Regarding Nektar’s stuff and Tobi [inhalable tobramycin], I’m curious what kind of device they’re using. You mentioned that it might be a high-resistance device, because you were interested in the effects of resistance on inhalation in children. But I thought their devices would tend to be low-resistance. I would expect their Exubera inhaled insulin device to be low-resistance. Would patients have trouble inhaling from it? What kind of DPI are they using?

Geller: To deliver Exubera they use an active DPI that produces the aerosol for the patient, and the device includes a chamber that holds the aerosol until the patient inhales it. They’re not using that for DPI tobramycin.

They’re using a simple device that’s very similar to an Aerolizer or a Handi-haler, which contains a capsule that is punctured and you inhale the contents. It’s an intermediate-resistance device.

Atkins: I have a question about the TOBI study. Are there any negative aspects of delivering 50 mg of powder in a single dose?

Geller: We were one of the centers that did the pharmacokinetics trial to find out how many capsules would be equivalent to a regular Tobi dose. The most common adverse effect was cough. The patients had more cough with the powder than with the liquid aerosol. The problem is that, as investigators, we are used to our CF [cystic fibrosis] patients coughing. When they are taking their regular Tobi, I’m not

sure if we were watching them for cough. But with a large volume of powder like that, we were expecting cough, and I think we might have over-reported cough with the powder and under-reported it with the liquid aerosol. But that was the largest adverse effect. There wasn’t any substantial bronchospasm with Tobi.

Smaldone: Regarding coughing and the various CF devices, we’ve done a couple of studies where we sat patients in the laboratory and gave them Pulmozyme or some other nebulized medication over 20–30 minutes, depending on how long it took for them to take the drug, and coughing has not been a problem for us. We pay attention to cough, because we can’t scan them when they’re jumping around coughing. So I believe there is a dif-

ference between different delivery systems with regard to cough, because of the distribution of particles and the concentration of particles per breath. With the DPI you get a lot more particles per breath, and I believe that cough is related to the concentration of particles in the aerosol, the site of deposition, the time frame in which they are deposited, and the patient's reactivity.

Geller: I agree.

Smaldone: I think that nebulizer therapy with conventional wet nebulization, such as with a drug like Tobi, will deliver similar amounts of drug over a longer period of time, probably to slightly different airways than with the rapid inhalation from a DPI, and I would expect that coughing would be less. I don't think that coughing is a major problem in routine nebulizer treatment with CF patients.

Geller: I think you're right. I think we still under-reported it, but I think about 60% of the patients coughed with the powder, because it was a lot of powder.

Smaldone: I would expect that coughing with a powder, but I don't

think that 60% of patients routinely cough during nebulizer therapy. We've looked at it in a wide range of patients with a wide range of function.

Geller: The pharmacokinetics were the same with 4 capsules or 112 mg of DPI Tobi as it was for a 300-mg Tobi dose.

Smaldone: That's very interesting data, and I think it would strongly support the use of the drug. I'm not saying you shouldn't use it. But with regard to coughing, I think the technique of delivery and the preparation are important.

Geller: You are absolutely right. Some of the patients had used DPIs before, but the amount of powder in an inhaler such as a Diskus is very small, compared to the large payload of 4 capsules. The DPI Tobi dose was about 112 mg to equal the deposition of 300 mg of wet nebulizer Tobi. The decrease in administration time was terrific. I think that the patients loved it even though they coughed.

Smaldone: I agree, and I think the coughing might not change the dose,

because studies have shown that once you deposit particles, many of them may not be coughed out.¹ I think there is a difference in the amount of coughing that occurs with various devices.

REFERENCE

1. Bennett WD, Chapman WF, Gerrity TR. Ineffectiveness of cough for enhancing mucus clearance in asymptomatic smokers. *Chest* 1992;102(2):412-416.

Fink: Regarding coughing, as we looked at insulin systems and at reported levels of cough among devices, it appeared there was a higher instance of cough in the reported work with the powder formulations. I looked at the literature on a few of the drugs that are available in both powder and nebulizer formulations, and it seemed that a higher percentage of cough was reported with the powder than with nebulizer formulations.

Geller: Several years ago we did a study to compare delivery of dornase alfa to CF patients with 2 different nebulizers, and I think the incidence of cough there was about 25% with a 2-3 minute treatment. It can happen. Some of these patients cough a lot.