

New devices for asthma

Donald P. Tashkin, MD *Los Angeles, Calif.*

The major antiasthma drugs currently are prescribed most often in aerosol form, with the use of a variety of inhaled-drug delivery devices. The 20th century has seen the evolution of ever more sophisticated aerosol delivery devices from the crude, medicated mist generators of questionable efficacy developed in the 19th century, to small-volume nebulizers, to the latest generation of metered-dose inhalers (MDIs) and dry-powder inhalers (DPIs).¹ It is hoped that further refinements in these devices will occur in the 21st century to make aerosol drug delivery even more efficient and convenient, as well as environmentally friendly. MDIs are currently the most widely used aerosol delivery devices. Over the last two decades, auxiliary devices for MDIs have been developed, such as spacers or aerosol holding chambers, to overcome problems associated with press-and-breathe MDI use. In addition, a growing interest has emerged in microelectronic monitoring devices to help physicians and patients monitor their own inhaler use, to assess and improve compliance, and, at least with one device, to optimize drug delivery from MDIs.

The purpose of this review is to provide a broad overview of both current and experimental devices for use in asthma and a brief discussion of what improvements are needed in such devices as we enter the new century.

INHALED-DRUG DELIVERY DEVICES

Nebulizers

Currently available small-volume nebulizers are mostly of the jet type. Plastic jet-type solution nebulizers are based on the Bernoulli principle and are powered by compressed gas from either electrically driven compressors or compressed gas cylinders. Before the advent of the MDI, portable glass nebulizers were manually powered by rubber hand bulbs for ambulatory use. Less widely used are small-volume ultrasonic nebulizers in which the liquid aerosol is generated by the vibrations of a piezoelectric crystal; the relative efficiency and reliability of ultrasonic nebulizers in delivering aerosolized medication require further evaluation.

Solution nebulizers have a number of advantages over MDIs. Unlike the latter, no special timing or coordination is needed. Because minimal patient cooperation is required, nebulizers are often the preferred inhalation

Abbreviations used

BDP:	Beclomethasone dipropionate
BOI:	Breath-Operated Inhaler
CFC:	Chlorofluorocarbon
DPI:	Dry-powder inhaler
HFA-134a:	Hydrofluoroalkane 134a
MDI:	Metered-dose inhaler
NES:	Nonelectrostatic spacer

device in infants and for treatment of acute severe asthma in emergency departments and the hospital. On the other hand, the dose delivered to the lung is dependent on the patient's breathing pattern—slow, deep inhalations being more efficient than rapid, shallow breathing. Another advantage is that in contrast to MDIs, no propellant is required. Also, theoretically at least, a variety of water-soluble agents can be aerosolized. In practice, however, only a limited number of drugs are available with relatively low topical-to-systemic activity for nebulized use in asthma, including β -agonists, anticholinergic bronchodilators, cromolyn, and some corticosteroid preparations. Moreover, although large doses of medication can be delivered conveniently and, if necessary, continuously by solution nebulizers, a very large fraction of these doses is wasted, mainly because of rain-out in the nebulizer and tubing. As a result, the respirable dose that is actually delivered to the patient is usually no greater than that delivered from a conventional MDI.²

Disadvantages of nebulizers include their bulk and expense, including a one-time expense for purchase of the equipment and the greater ongoing cost for equivalent doses of medication in solution form compared with an MDI. Nebulizers are also less convenient than MDIs, requiring frequent cleaning and more time for dispensing medication, depending on the volume of solution added to the nebulizer (approximately 10 minutes to deliver a conventional therapeutic dose of a bronchodilator with a fill volume of 3 ml). A major disadvantage is the wide variability in the output characteristics of different nebulizers that is influenced mainly by nebulizer brand and, to a lesser extent, fill volume, flow rate, and humidity of the compressed gas used to power the nebulizer (Fig. 1).² As a result, the particular dose that is nebulized is difficult to predict. Furthermore, nebulizers are generally far less efficient than MDIs, with MDI-to-nebulizer efficiency ratios of as high as 1:12.5 times.³ For example, 2.5 mg albuterol added to a nebulizer may yield a respirable mass delivered to the patient as low as 0.2

From the Division of Pulmonary and Critical Care Medicine, University of California at Los Angeles School of Medicine.

Reprint requests: Donald P. Tashkin, MD, UCLA School of Medicine, Department of Medicine, 10833 Le Conte Ave., Los Angeles, CA 90095-1690.

J Allergy Clin Immunol 1998;101:S409-16.

Copyright © 1998 by Mosby, Inc.

0091-6749/98 \$5.00 + 0 1/0/86481

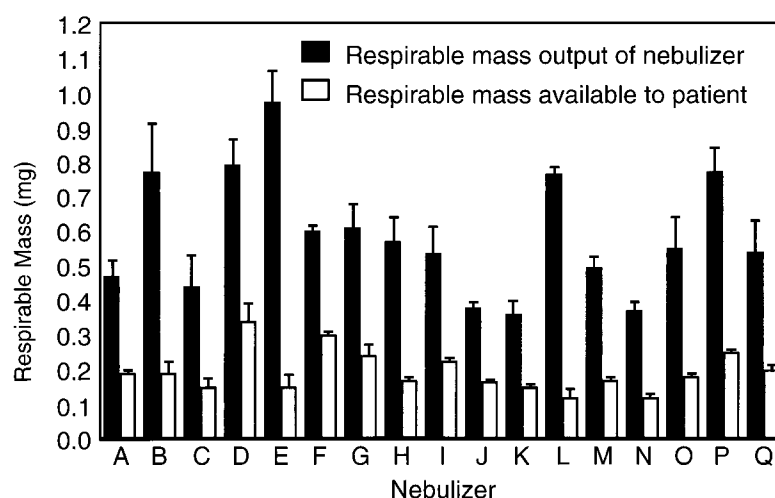


FIG. 1. Effect of nebulizer brand on respirable mass output of nebulizer (closed bars) and respirable mass available to patient (open bars). Adapted with permission from Hess D, Fisher D, Williams P, Pooler S, Kacmarek RM. *Chest* 1996;110:498-505.

mg, which is approximately equivalent to two inhalations from an albuterol MDI (90 µg/inhalation).

Press-and-breathe MDIs

The MDI had its debut 40 years ago with the advent of Medihaler-Iso and Medihaler-Epi (3M Pharmaceuticals, St. Paul, Minn.). The MDI consists of micronized drug in suspension or solution (with ethanol as the cosolvent), together with one or more chlorofluorocarbon (CFC) propellants pressurized within an aluminum canister or glass bottle. A surfactant is also present to lubricate the valve and keep the drug particles in suspension (for suspension formulations). Each metered dose of the drug is delivered from a metering chamber when the canister is depressed into the actuator or mouthpiece; this action results in decompression of the formulation within the valve's metering chamber, resulting in the explosive generation of a heterodisperse aerosol of droplets that consist of tiny drug particles contained within a shell of propellant. The latter evaporates with time and distance, which reduces the size of the particles; typically, approximately 40% to 50% of the particles are within the respirable range (< 5 µm).

MDIs have a number of major advantages that have made them currently the most widely used inhaled-drug delivery device. They are compact, portable, rugged, and simple to use. Since 1956, the number of drugs available for delivery from an MDI has expanded to include the major classes of antiasthma drugs, including short-, intermediate-, and long-acting β_2 -selective agonists, a quaternary anticholinergic bronchodilator, cromolyn, nedocromil, and a number of inhaled corticosteroids. MDIs have a multidose capacity of 100 to 400 doses per canister. Dosing is rapid and convenient, with delivery of therapeutic doses in two inhalations or less. A large fraction of the aerosol particles is in the respirable

range, and dosing is, in general, highly reproducible from puff to puff.

The major disadvantage of MDIs is that efficient dosing is highly technique dependent, requiring proper hand-lung coordination (for press-and-breathe devices), slow, deep inhalation (inhaled flow of ≈ 0.4 L/min) to prevent premature impaction of aerosol particles in central airways due to turbulent flow, and a long breath-holding time (≥ 10 seconds) to allow sufficient time for deposition of submicronic inhaled particles in the lung by gravitational sedimentation.^{4,5} Errors in technique are unfortunately common, as is poor compliance with inhaler use. Other disadvantages include occasional "loss of prime" (i.e., loss of a complete dose when the inhaler is stored for some time due to draining of the formulation from the valve's metering chamber) and nonabrupt tail-off (i.e., wide, unpredictable fluctuations in the dispensed dose when the MDI is nearly empty). These phenomena can result in unreliable and ineffective dosing to the patient. Another disadvantage is the absence of built-in counters that would alert the patient to the fact that the inhaler was approaching "empty" and needed to be refilled. Although relatively infrequent, local side effects can also result from MDI use, including mild throat irritation, mouth dryness, cough, "paradoxical" bronchospasm, and, with inhaled corticosteroids, dysphonia and oropharyngeal candidiasis.

Another important disadvantage of MDIs is that with the exception of one product (Proventil-HFA, Key Pharmaceutical, Kenilworth, N.J.), all current MDIs use CFCs (mostly CFC-11 and CFC-12) as the propellant system. CFCs are not degraded in the lower atmosphere and rise to the stratosphere, where they have a long residence time (50 to 100 years) and exert a greenhouse effect, trapping the earth's heat and contributing to global warming. Eventually, CFCs are broken down by

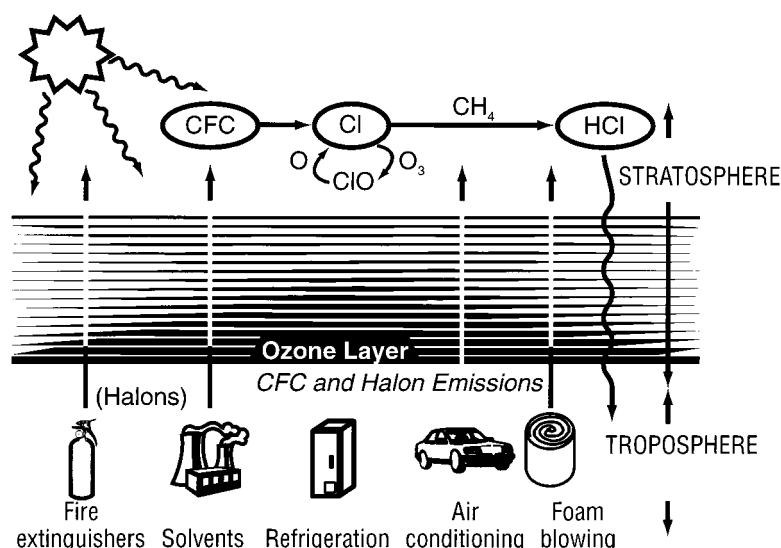


FIG. 2. Breakdown of CFCs by solar radiation releases active chlorine fragments that destroy ozone. Adapted with permission from Hayman G. *Br J Clin Pract* 1995;79:2-6.

solar radiation, releasing active chlorine radicals that are highly active in destroying ozone (one chlorine fragment destroys 100,000 ozone molecules) (Fig. 2).⁶ Over the past two decades, total ozone amounts measured using satellites equipped with ozone-mapping spectrophotometers have documented increasing depletion of the ozone layer in the stratosphere, mainly over Antarctica but also over heavily populated regions of the earth. This progressive ozone depletion, which has been linked to increasing amounts of CFCs in the stratosphere, has potentially grave clinical implications with respect to the risk of skin cancer and cataracts. Accordingly, more than 130 nations have signed the Montreal Protocol, an international treaty that set worldwide goals for phased reduction and eventual elimination of CFC use. Exemptions are currently being made for essential uses that are critical to health, including MDIs for asthma and chronic obstructive pulmonary disease in the absence of alternative propellants or delivery systems.

In response to the ozone depletion crisis, the pharmaceutical industry is actively developing alternatives to CFC-MDIs, including MDIs with a non-CFC propellant that is ozone-friendly and has no or minimal greenhouse effect and DPIs, which require no propellant. Hydrofluoroalkane 134a (HFA-134a) is an alternative propellant that contains no chlorine (and thus does not cause free-radical ozone destruction) and has a short residence time of approximately 15 years in the stratosphere, so that it has substantially less global warming potential than do CFCs. HFA-134a albuterol (Proventil-HFA) is the first HFA-MDI that has received approval in both Europe and the United States. This preparation consists of albuterol suspended in HFA-134a, oleic acid, and ethanol. It has the same particle-size distribution as CFC-albuterol, and clinical trials have shown this preparation to be bioequivalent in both bronchodilator effi-

cacy (Fig. 3) and side effects (e.g., heart rate increase, hypokalemia) (Fig. 4).⁷ The reformulation of albuterol in an alternative propellant provided the opportunity to improve the MDI valve design, resulting in such advantages as no loss of prime, an abrupt tail-off, and a smaller valve size (25 μ l) than the standard MDI. These improvements would be expected to increase the reliability of dosing and the velocity of the aerosol, potentially reducing oropharyngeal deposition and improving delivery to the lung.

Not all inhaled antiasthma drugs can readily be reformulated in HFA-MDIs. For example, beclomethasone dipropionate (BDP) is not suspendable in HFA-134a. However, it is stable in a solution formulation with HFA-134a, ethanol, and a surfactant. Interestingly, an MDI with this formulation dispenses an aerosol that has a particularly small particle size (mass median aerodynamic diameter $\approx$ 1 μ m, which is less than that of CFC-formulated BDP). Thus a metered dose of BDP from an HFA-MDI should result in an increased respirable mass, an increased dose delivered to the lung (and possibly to smaller airways, in particular), and decreased oropharyngeal deposition, compared with the same dose of BDP from a CFC-MDI.

DPIs

DPIs are another environmentally friendly alternative to CFC-MDIs. DPIs consist of drug in powdered form that has been milled to produce micronized particles in the respirable range. The delivery device allows the particles to be deagglomerated by the energy created by the patient's own inspiratory flow or, in the case of one device under development, by a battery-operated impeller. The powdered drug can be either pure (as in the Turbuhaler, Astra AB, Sweden) or blended with lactose as a carrier powder (as in the Diskhaler, Allen &

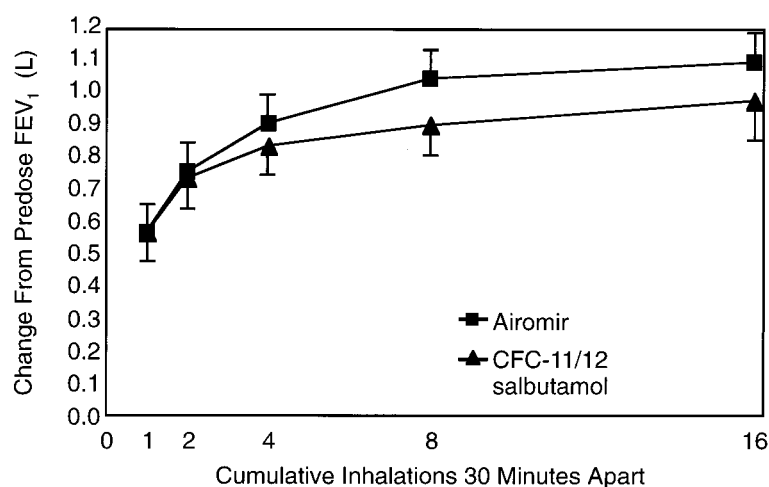


FIG. 3. Cumulative dose response of salbutamol sulfate in CFC-free system versus CFC-salbutamol in patients with asthma ($n = 24$). Mean ($\pm$ SE) change from predose FEV_1 . *Airomir*, salbutamol sulfate in CFC-free system. Adapted with permission from Tashkin D. Br J Clin Pract 1995;79:33-4.

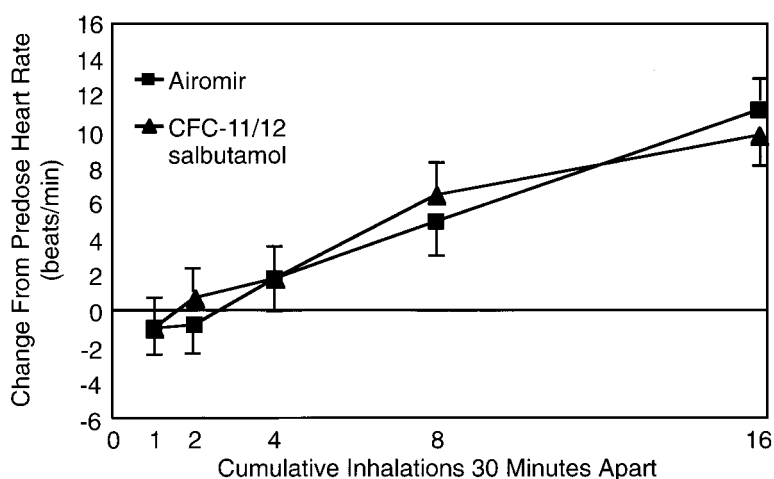


FIG. 4. Cumulative dose response of salbutamol sulfate in CFC-free system versus CFC-salbutamol in patients with asthma ($n = 24$). Mean ($\pm$ SE) change from predose heart rate. *Airomir*, salbutamol sulfate in CFC-free system. Predose heart rate for salbutamol sulfate in CFC-free system patients was 76.0 ± 9.0 beats/min and for CFC-salbutamol patients was 74.4 ± 8.7 beats/min. Adapted with permission from Tashkin D. Br J Clin Pract 1995;79:33-4.

Hanburys Ltd., United Kingdom, Rotahaler, Allen & Hanburys, Research Triangle Park, N.C. or Spinhaler, Fisons Corporation, Rochester, N.Y.).

The advantages of DPIs are that they are breath-actuated, requiring minimal patient coordination. Like the MDI, they are relatively simple, compact, and portable, but, unlike the MDI, there is no need for a CFC or alternative propellant system. Moreover, the empty condition is apparent, alerting the patient to the need for replacement. The newer DPIs (not yet available in the United States) have a multidose capacity.

DPIs also have several disadvantages. For example, some DPIs require relatively high flow rates (≈ 60 L/min) to deagglomerate the powder and thus present

difficulties for some children and patients with severe bronchospasm. Dependency of the dose on the inspiratory flow rate is a problem with certain DPIs, resulting in lack of predictable dosing, increased puff-to-puff dosage variability, and deviation from the nominal dose. For example, the terbutaline Turbuhaler yielded less than 8.9% respiratory deposition when it was inhaled with a flow rate of 15 L/min, compared with greater than 35% deposition when it was inhaled with a flow rate of 60 L/min.⁸ Moreover, the amount of budesonide deposited in the lung (estimated from the amount absorbed systemically after subtracting the swallowed dose) from a Turbuhaler was twice that absorbed from the lung when the same total dose ($\approx 900 \mu\text{g}$) was inhaled from a

pressurized MDI.⁹ Other disadvantages of DPIs include agglomeration of the particles of powder by high humidity that reduces the delivered dose, technical difficulty for certain patients in operating some types of DPIs, and the current availability of only inconvenient single-dose units (e.g., albuterol Rotahaler) in the United States.

The problem of inspiratory flow rate dependence is being addressed through the development of newer DPIs that overcome this difficulty. For example, the power-assisted DPI under development by Dura Pharmaceuticals (Dura Spiros, Dura Pharmaceuticals, San Diego, Calif.) incorporates a battery-powered, twin-blade impeller that is actuated by a minimal inspiratory flow rate to rotate at more than 15,000 rpm. The action of the impeller generates a consistent powder aerosol that is relatively independent of inspiratory flow.¹⁰

Breath-actuated MDIs

Breath-actuated MDIs have been developed to overcome the difficulty with hand-lung coordination posed by conventional press-and-breathe MDIs. Examples of breath-actuated MDIs that are available in the United States and/or the United Kingdom include the Autohaler (3M Pharmaceuticals, St. Paul, Minn.) and the Breath-Operated Inhaler (BOI, Baker Norton, United Kingdom). The Autohaler dispenses pirbuterol (available in the United States) or beclomethasone (not available in the United States). It has a manually operated lever that, when lifted, primes the inhaler through a spring-loaded mechanism, allowing the aerosol to be dispensed with a modest inspiratory flow (≈ 30 L/min) at the mouthpiece.¹¹ Clinical studies have demonstrated that the use of the pirbuterol Autohaler is easy to teach¹² and results in lung deposition equivalent to that produced by a properly used conventional MDI and greater lung deposition than that resulting from conventional MDIs in patients with poor coordination.¹¹ Moreover, it can be used effectively by patients with poor lung function,¹³ patients with arthritis and limited manual dexterity,¹⁴ and elderly patients.¹⁵

An albuterol BOI is currently under investigation in the United States. This device consists of a standard MDI cannister inserted in the BOI. The latter contains a pneumatically operated, spring-loaded firing mechanism that is primed by opening a hinged mouthpiece. The metered dose of albuterol is released when a flap valve is opened on inspiration from the device with a flow rate of 25 L/min. In vitro studies have shown that aerosolized doses of albuterol BOI have the same characteristics (i.e., unit-actuator dose, particle-size distribution, respirable fraction) as those of the Ventolin (Allen & Hanburys, Research Triangle Park, N.C.) MDI, but comparative clinical efficacy data are not yet available. A similar device (Easi-Breathe, Baker Norton, United Kingdom) that dispenses salbutamol (albuterol) and beclomethasone is in use in the United Kingdom and Ireland, and one that dispenses cromolyn is awaiting approval.

SPACERS

A variety of spacers and aerosol holding chambers have been introduced over the past one to two decades to reduce problems of poor hand-lung coordination associated with press-and-breathe MDIs and to minimize local complications of MDI aerosols by reducing oropharyngeal deposition. By acting as an aerosol reservoir, these auxiliary devices slow the aerosol jet velocity and increase transit time and distance between the MDI actuator and the mouth, allowing particle size to decrease. As a result, the respirable portion of the dose is increased, thus favoring improved delivery of the submicronic aerosol particles to the lung periphery. Moreover, because these devices trap large particles comprising up to 70% to 80% of the aerosol dose, only a small fraction of the dose is deposited in the oropharynx, thereby diminishing such side effects as throat irritation, dysphonia, and thrush associated with inhaled corticosteroid aerosols delivered by MDIs. Finally, some devices are equipped with special valves that provide audible cues to patients to inhale more slowly; these devices generate a whistling sound when inspiratory flow rates exceed a threshold value (e.g., 0.4 L/sec), above which turbulent conditions lead to excessive impaction of the aerosol dose in the upper or central airways.

A wide variety of different types of spacers and aerosol holding chambers are commercially available. These differ in a number of physical characteristics, including volume (i.e., 113 to 750 ml), length (i.e., 9 to > 30 cm), shape (i.e., cylinder, cone, pear, sphere), construction material (i.e., plastic, metal), rigidity (i.e., rigid, extendable, collapsible), valve system (i.e., present/absent, with or without separate valves for inspiration and expiration, dead space) and electric charge (e.g., with: plastic; without: metal). In addition, some spacers can be provided with different interfaces with the airway opening (e.g., mouthpiece, face mask, adaptor to ventilator tubing). Several studies have demonstrated the effectiveness of a bronchodilator MDI with a valved holding chamber in treating pediatric asthma as well as severe acute asthma in both children and adults in the emergency department.¹⁶ Advantages of an MDI with a holding chamber over a nebulizer include improved delivery efficiency, greater convenience, greater speed of administration, greater cost-effectiveness, an inherently lower risk of pulmonary infection, and the unavailability of approved topically active corticosteroid solutions for inhalation from wet nebulizers.

The varying characteristics of different types of spacers (i.e., volume, length, shape, valves, electrostatic charge) might be expected to affect the respirable dose delivered from the MDIs to which these spacers are interfaced. For example, Bisgaard et al¹⁷ showed that the dose of budesonide from an MDI delivered to infants differed by up to as much as twofold, depending on the type of spacer used; a metallic, pear-shaped nonelectrostatic spacer (NES) with separate inspiratory and expiratory valves with no dead space delivered the highest dose, followed in descending order of efficiency by the

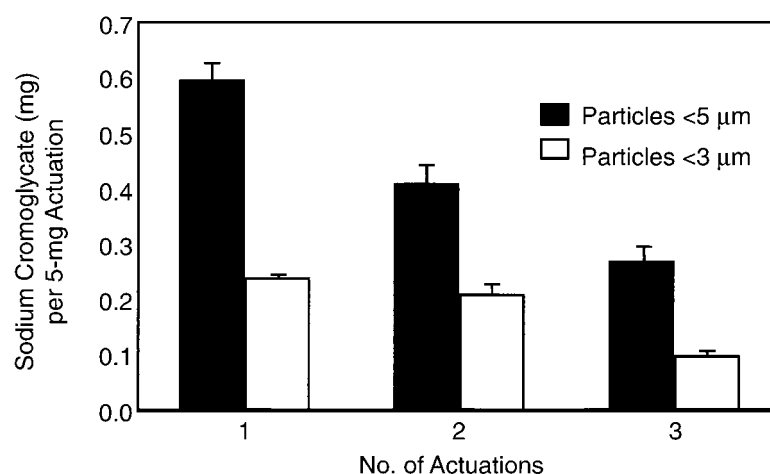


FIG. 5. Effect of multiple MDI actuations into spacer on amount of drug available per puff. Adapted with permission from O'Callaghan C, Lynch J, Cant M, Robertson C. *Thorax* 1993;48:603-6.

Babyhaler (GlaxoWellcome, United Kingdom) (a 350 ml plastic cylinder with both inspiratory and expiratory valves with a 40 ml dead space), the Nebuhaler (Astra AB, Sweden) for babies (a 750 ml plastic, pear-shaped device with an inactivated valve system), and the AeroChamber (Forest Pharmaceuticals, Inc., St. Louis, Mo.) (a 145 ml plastic cylinder with a single, one-way valve). These differences in dosing efficiency were thought to be due to less electrostatic attraction of charged aerosol particles to the walls of the NES and the no dead-space, separate inspiratory and expiratory valve design of the NES. Agertoft and Pedersen¹⁸ found that budesonide was delivered from an MDI attached to a Nebuhaler (750 ml) or a Babyspacer (200 ml, 23 cm) with similar efficiency, implying that volume alone was not necessarily an important determinant of spacer performance. On the other hand, the shorter AeroChamber (< 10 cm) was the least efficient, which suggests that a critical length might be important for maximal efficiency. In both of these studies, each actuation of the MDI into the spacer was followed by a 30- to 60-second period of inspiring from the holding chamber. Therefore, the volume of the spacer may not have influenced dosing efficiency because the total ventilation over 30 to 60 seconds was sufficient to clear the aerosol from the entire volume of the spacer, even for young children with very low tidal volumes.

Add-on spacers do not completely obviate errors in MDI technique. For example, as with MDIs without a spacer, patients using MDIs with spacer attachments still have to be trained to inhale slowly (≤ 30 L/min) and to hold their breath after aerosol inhalation for 10 seconds or more. Also, although spacers may eliminate the need for split-second timing in hand-lung coordination, too long a delay in inhalation after actuation can lead to excessive loss of the respirable dose within the device. For example, a delay as long as 5 to 10 seconds can reduce the effective dose by approximately 50%.¹⁹ Fur-

thermore, some patients tend to discharge multiple doses from an MDI into a spacer before inhalation. The turbulence created by this practice leads to coalescence of small particles into larger particles and excessive deposition on the walls of the spacer, thus effectively reducing the respirable dose per actuation. For example, O'Callaghan et al.¹⁹ found that two actuations of cromolyn into a spacer reduced the respirable dose per puff by approximately one third and three actuations reduced the respirable dose per puff by one half (Fig. 5).

Similarly, Barry and O'Callaghan²⁰ found that compared with the MDI alone, one actuation of an albuterol MDI from a spacer reduced the dose to the patient by approximately one third, two actuations by 45%, and three actuations by 75%. Finally, different spacers may perform differently, depending on the particular MDI with which they are used. Ahrens and coworkers²¹ measured the fine particle dose of albuterol, bitolterol, flunisolide, and beclomethasone delivered with the MDI alone and through four different holding chambers (ie, Ace, Diemolding Healthcare Division, Canastota, N.Y., Optihaler, Health Scan Products, Inc., Cedar Grove, N.J., AeroChamber, Forest Pharmaceuticals, Inc., St. Louis, Mo., InspirEase, Selering Corporation, Kenilworth, N.J.). They found an interesting interaction between the type of MDI and the type of spacer, such that the respirable dose delivered from the same MDI varied with the type of spacer used. For example, compared with the MDI alone, for flunisolide the respirable dose was substantially reduced with all spacers tested except the AeroChamber; whereas for beclomethasone, the fine-particle dose was reduced with all spacers except the InspirEase.²¹ These findings suggest the need for further studies to evaluate the interaction between specific MDIs and the individual types of spacers with which they are used. For particular MDI-spacer combinations, the respirable dose delivered from the spacer must be defined.

MICROELECTRONIC MONITORING DEVICES

Compliance with prescribed use of inhalers for asthma control is often poor. The consequences of poor inhaler compliance include (1) treatment failure resulting in increased asthma morbidity and personal and public expense for health care, (2) unnecessary intensification of therapy, potentially leading to complications from overmedication, and (3) inaccurate interpretation of results from clinical trials.²² Methods of assessing inhaler compliance include the following: (1) clinical judgment, (2) self-report, (3) medication measurement (e.g., canister weights, tracking prescription refills), (4) biochemical validation, and (5) microelectronic medication monitoring. However, clinical judgment is often unreliable, self-report notoriously overestimates compliance, canister weights provide no information of the pattern of inhaler use, and biochemical validation of self-reported drug use is generally not feasible for inhaled agents. Microelectronic medication monitoring is the most accurate method of objectively assessing inhaler compliance. Moreover, previous studies have shown that microelectronic devices are useful not only for assessing compliance²³ but also for enhancing compliance if the microelectronic information is "fed back" to patients to provide positive reinforcement of the physician-prescribed treatment regimen.²⁴

Three types of microelectronic medication monitors are currently available for assessing inhaler compliance: the MDI Chronolog (Med Trac Technologies, Lakewood, Colo.), the Doser (NewMed Corporation, Billerica, Mass.), and the Smartmist (Aradigm Corporation, Hayward, Calif.). The MDI Chronolog is a small, portable electronic device that houses an MDI canister. Each actuation of the canister results in a small temperature change that is sensed by a thermistor in the chronolog. The chronolog memory records and stores the date and clock time of each actuation up to 2000 actuations and is read out by an IBM PC in day-hour-minute format as well as by graphic illustration with a special computer interface and display software. Advantages of the MDI Chronolog are that it tracks the date and clock time of each actuation, the data are downloadable, a large amount of data can be stored in computer memory, and the device is rugged and relatively compact. Disadvantages are that it is relatively expensive, special mouthpiece adaptors are required for different MDIs and may influence aerosol delivery, the device does not provide any ongoing direct feedback to patients, and electronic misregistration and data loss caused by hardware and software problems are not uncommon.

The Doser is a novel, inexpensive, commercially available microelectronic monitoring device that when attached to an MDI, has the capability of providing continuous feedback to patients of their actual daily patterns of inhaler use. The device fits on the flat end of the MDI and is sensitive to the pressure used to depress the canister during each use of the inhaler, recording each use in its electronic memory. The

device displays three measures of daily MDI use in light-emitting diode displays on its face: (1) the daily total number of actuations, (2) the number of doses remaining in an attached MDI (an audible beep signals when the canister is nearly empty), and (3) the daily total of actuations stored in memory for each of the preceding 45 days for later recall. The Doser has the following advantages: It provides daily feedback directly to patients, thus reminding them to take the prescribed number of puffs on any day and potentially enhancing daily compliance; it tracks the medication left in the canister, thereby signaling when the MDI is nearly empty and needs to be refilled; it is relatively inexpensive; it is small and compact; it is adaptable to nearly all press-and-breathe MDIs; it is compatible with spacers; and it does not interfere with drug delivery. Although potentially very useful, the Doser has a few disadvantages: "Set-up" of the device may be difficult for technophobic patients; data are not downloadable in the current version, thus making its use for clinical investigation more cumbersome; it has a relatively short memory (45 days); occasional misregistration of actual inhaler uses occur; it needs to be "reset" for each new inhaler; and it needs to be replaced after 1 year. Moreover, although the current versions of both the MDI Chronolog and the Doser are able to track each actuation of the inhaler, neither of these two devices can record whether the dose discharged from the MDI was actually inhaled.

The SmartMist is a handheld, breath-activated device with a built-in pneumotachygraph and microprocessor. The MDI is inserted into the device, whose microprocessor can be programmed to deliver each inhaler dose at a predetermined point during inhalation from the MDI, as defined by both the inspiratory flow rate (e.g., 0.4 L/sec) and the inspired volume that has accumulated from the onset of inspiration (e.g., 0.2 L).²⁵ In addition, light-emitting diodes provide visual feedback to the patient. Thus the device can serve to optimize MDI use technique. No drug is delivered unless both flow and volume criteria are met. Although these features may be frustrating for patients who have failed to master proper technique but require dosing from the MDI for relief of acute bronchospasm, the MDI can be manually removed from the device for conventional use in an emergency. The information concerning different aspects of inhaler use (i.e., frequency, volume, and flow during use) is stored in the memory of the device, downloadable, and retrievable by a personal computer. In addition to its capability of monitoring the frequency and temporal pattern of inhaler use, as well as actual inhalation of the MDI dose, advantages of the SmartMist include its unique ability to ensure that the MDI is being used optimally and to help train patients in the proper technique of MDI use. Its major disadvantage is its expense, which limits its broad applicability. However, this device may be cost-effective for the subset of patients who are particularly difficult to train to use MDIs correctly.

CONCLUSIONS

The 21st century will undoubtedly see further advances in devices for delivering inhaled medication to asthmatic patients and for monitoring and assisting adherence to prescribed inhaler use. The challenges for the 21st century will be (1) to develop more formulations in environmentally safe, alternative propellants (e.g., HFA-134a) for pressurized MDIs, (2) to develop improved breath-actuated MDIs that deliver the full range of inhaled asthma medications, (3) to develop user-friendly "spacers" that are specific to particular MDIs and to evaluate the delivery of respirable doses from these spacer-inhaler combinations, (4) to refine multi-dose DPIs to maximize convenience and minimize problems of inspiratory flow-rate dependence and excessive oropharyngeal deposition, (5) to develop and encourage the use of new, inexpensive, user-friendly microelectronic monitoring devices to help patients track inhaler use and enhance compliance, and (6) to improve the education of physicians, other health professionals, and patients regarding the proper use of inhalers, spacers, and other auxiliary devices for asthma. Reduction in asthma morbidity and mortality in the next century will depend in large part on how successfully these challenges are met.

REFERENCES

- Grossman J. The evolution of inhaler technology. *J Asthma* 1994; 31:55-64.
- Hess D, Fisher D, Williams P, Pooler S, Kacmarek RM. Medication nebulizer performance: effects of diluent volume, nebulizer flow and nebulizer brand. *Chest* 1996;110:498-505.
- Tashkin DP. Dosing strategies for aerosol delivery to the airways. *Respir Care* 1991;36:977-88.
- Newman SP, Pavia D, Clarke SW. How should a pressurized beta-adrenergic bronchodilator be inhaled? *Eur J Respir Dis* 1981; 62:3-20.
- Newman SP. Aerosol generators and delivery systems. *Respir Care* 1991;36:939-51.
- Hayman G. Why the environment matters. *Br J Clin Pract* 1995;79: 2-6.
- Tashkin D. Cumulative dose-response study of Airomir (salbutamol sulphate in CFC-free system) versus CFC salbutamol in patients with asthma. *Br J Clin Pract* 1995;79:33-4.
- Newman SP, Moren F, Trofast E, Talaei N, Clarke SW. Terbutaline sulphate Turbuhaler effect of inhaled flow rate on drug deposition and efficacy. *Int J Pharmaceutics* 1991;74:209-13.
- Thorsson L, Edsbacker S, Conradson T-B. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. *Eur Respir J* 1994;7:1839-44.
- Hill M, Vaughan L, Dolovich M. Characteristics of an active, multiple-dose, dry powder inhaler. In: Bryon PR, Dolby RN, Farr SJ, editors. *Respiratory drug delivery V*. Buffalo Grove, Ill: Interpharm Press, Inc; 1996. p. 197-208.
- Newman SP, Weisz AWB, Talaei N, Clarke SW. Improvement of drug delivery with a breath actuated pressurized aerosol for patients with poor inhaler technique. *Thorax* 1991;46:712-6.
- Crompton G, Duncan J. Clinical assessment of a new breath-actuated inhaler. *Practitioner* 1989;233:268-9.
- Fergusson RJ, Lenney J, McHardy GJR, Crompton GK. The use of a new breath-actuated inhaler by patients with severe airflow obstruction. *Eur Respir J* 1991;4:172-4.
- Arthur V, Pushkin S, Emery P. Inhaler use in patients with arthritic hands. *Clin Trials Meta-Anal* 1992;28:23-8.
- Diggory P, Bailey R, Vallon A. Effectiveness of inhaled bronchodilator delivery systems for elderly patients. *Age Aging* 1991;20:379-82.
- Benton G, Thomas RC, Nickerson BG, McQuitty JC, Okikawa J. Experience with a metered-dose inhaler with a spacer in the pediatric emergency department. *Am J Dis Child* 1989;143:678-81.
- Bisgaard H, Anhoj J, Klug B, Berg E. A non-electrostatic spacer for aerosol delivery. *Arch Dis Child* 1995;73:226-30.
- Agertoft L, Pedersen S. Influence of spacer device on drug delivery to young children with asthma. *Arch Dis Child* 1994;71:217-20.
- O'Callaghan C, Lynch J, Cant M, Robertson C. Improvement in sodium cromoglycate delivery from a spacer device by use of an antistatic lining, immediate inhalation, avoiding multiple actuations of drug. *Thorax* 1993;48:603-6.
- Barry PW, O'Callaghan C. Multiple actuations of salbutamol MDI into a spacer device reduce the amount of drug recovered in the respirable range. *Eur Respir J* 1994;7:1707-9.
- Ahrens R, Lux C, Bahl T, Han S-H. 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.
- Tashkin DP. Multiple dose regimens: impact on compliance. *Chest* 1995;107:176S-82S.
- Rand CS, Wise RA, Nides M, Simmons MS, Bleeker ER, Kusch JW, et al. Inhaler adherence in a clinical trial: comparison of self-report and canister weighing to the nebulizer chronolog. *Am Rev Respir Dis* 1992;146:1559-64.
- Nides MA, Tashkin DP, Simmons MS, Wise RA, Li VC, Rand CS. Improving inhaler adherence in a clinical trial through the use of the nebulizer chronolog. *Chest* 1993;104:501-7.
- Farr SJ, Rowe A, Rubsamen R, Tayler G. Aerosol deposition in the human lung following administration from a microprocessor controlled pressurized metered dose inhaler. *Thorax* 1995;50:639-44.