

# Optimizing Aerosol Delivery by Pressurized Metered-Dose Inhalers

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### Summary

The modern era of aerosol therapy began with the introduction of the Medihaler Epi in 1956, after a 13-year-old asthmatic told her father, an officer in the Riker company, that asthma medications should be as convenient to use as hair spray and she complained that the bulb atomizer leaked in her school bag. Since then, advances in technology have made aerosol delivery much more efficient, so that it is now the most widely used mode of medication delivery for chronic airways diseases. Today the pressurized metered-dose inhaler (pMDI) is a metal canister containing a mixture of propellants, surfactants, preservatives, and drug. However, pMDIs are underused in the United States. One barrier to use is the misconception related to pMDI effectiveness relative to small-volume nebulizers, especially among pediatricians. This is despite the strongest evidence of pMDI superiority, from well-controlled pediatric studies. In this manuscript we discuss ways to optimize the use of medications given via pMDI and examine recent changes in pMDI technology that will make drug delivery more efficient and consistent. *Key words: metered-dose inhaler, MDI, aerosol, drug delivery.* [Respir Care 2005;50(9):1191–1197. © 2005 Daedalus Enterprises]

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## Introduction

The modern era of aerosol therapy began with the introduction of the Medihaler Epi in 1956.<sup>1</sup> Before that time, the only portable handheld aerosol delivery system was the bulb nebulizer, which gave poor and inconsistent pulmonary delivery. Since the 1950s, advances in aerosol technology have made aerosol delivery much more efficient, so that it is now the most widely used mode of medication delivery for chronic airways diseases.

Aerosol delivery has recently been reviewed by a panel of the American College of Chest Physicians.<sup>2</sup> In this evidence-based review it was determined that for most patients with asthma, nebulizers, dry powder inhalers (DPIs), and pressurized meter-dosed inhalers (pMDIs) were equally effective in delivering short-acting  $\beta$  agonists, if the device was used appropriately by the patient. Albuterol via pMDI has also been shown to be at least as effective as nebulized albuterol for the therapy of acute moderate-to-severe asthma episodes in children.<sup>3-7</sup>

Although the devices are equally effective if used correctly, there are important differences in the ability of individual patients to use them, as well as differences in costs, convenience, portability, and particle-generation characteristics.

## The Principles of pMDI Design

The story of the pMDI began in 1955, when a 13-year-old asthmatic told her father that asthma medications should be as convenient to use as her mother's hair spray, and she complained that the bulb atomizer leaked in her school bag. Susie was the daughter of Dr George Maison, the president of the Riker company. A 3-person development team, consisting of Maison, Charles Thiel, and Irving Porush, started with an old ice cream freezer, a case of empty perfume vials, a bottle capper, and some propellants from Dupont to produce the first pMDI prototype.<sup>8</sup> The pMDI evolved to include a 50- $\mu$ L metering device developed for the perfume industry, a 10-mL amber vial, and a plastic mouthpiece with molded nozzle to administer salts of isoproterenol and epinephrine. The first clinical trials began that same year at the Veterans Administration Hospital in Long Beach, California. In January of 1956, a new drug application was filed with the Food and Drug Administration and approved 2 months later. The next year, a surfactant and micronized powder were added to the propellant, creating the first commercially available formulation.<sup>1</sup> Today the pMDI is a pressurized metal canister containing a mixture of propellants, surfactants, preservatives, and drug. The drug represents about 1% of the contents, while the propellants are greater than 80% of the contents, by weight.

## Traditional Chlorofluorocarbon pMDIs

Chlorofluorocarbon (CFC) pMDIs have largely been incremental improvements over the original devices from the mid-1950s. With the demands of both newer medications and the requirements for new, non-ozone-depleting carriers, there have been more substantial changes in pMDI design and function in the past decade.

**Strengths.** The pMDI is convenient, lightweight, portable, multidose, and can be stored in any orientation without leakage. The pMDI reliably provides consistent dosing during the canister life.

The traditional pMDI is an inexpensive dosage form. In volume, the cost to produce a pMDI is less than \$2.00. This is much less expensive than any other aerosol device that has multidose convenience.

**Limitations.** The pMDI is not available for all drugs or dosages, making it difficult for clinicians to prescribe the same type of device for diverse inhaled medications.<sup>9</sup> This is exacerbated by the trend of many pharmaceutical companies not to release newer inhaled drugs as pMDIs. The design of the CFC-propellant pMDI requires initial and frequent priming. Failure to prime the device results in administration of a substantially lower dose than that prescribed.<sup>10</sup> Unfortunately, frequent priming tends to waste drug to atmosphere.

The greatest single limitation of the pMDI is the inconsistent dosing that occurs with incorrect use. This includes the impact of hand-breath asynchrony, excessive inspiratory flow velocity, nose-breathing, and the cold-Freon effect (the patient stops inhalation when the cold aerosol plume reaches the hypopharynx).<sup>11,12</sup> For an aerosol device efficiently to deliver medication to the lower respiratory tract, most of the aerosol medication particles must be of a size for inhalation and deposition in the airway, generally 0.5–4.5  $\mu$ m mass median aerodynamic diameter. The patient must inhale the aerosol with a slow, deep inhalation to maximize aerosol deposition in the airway, followed by a breath-hold to allow sedimentation of the medication particles.<sup>13</sup>

Extended use of the pMDI beyond the labeled number of doses results in a "tailing-off" effect at the end of canister life. While the pMDI provides consistent dosing for the number of actuations listed on the drug label, after that the dose fluctuates between the nominal dose and a negligible dose. In the absence of a dose-counter, which is not provided with most pMDIs, the patient must count the number of doses taken to determine the effective life of the pMDI. The method of "floating" the pMDI canister in water to determine canister depletion is unreliable, and water entering the nozzle can reduce the emitted dose of subsequent actuations.<sup>14</sup>

Environmental factors such as temperature contribute to inconsistent doses. As the temperature of the canister drops, so does the emitted dose of the CFC pMDI. This is the basis of recommendations to warm the pMDI canister to hand temperature prior to use.<sup>15,16</sup> Heating the canister beyond body temperature may increase the emitted dose.

### Hydrofluoroalkane pMDIs

There is a zone about 10–25 miles above the earth's surface in which ozone is relatively highly concentrated. Once released, CFCs rise to the stratosphere, where they are gradually broken down by ultraviolet light to release chlorine, which depletes stratospheric ozone. This leads to higher ultraviolet-B radiation levels, which increases the risk of skin cancer and cataracts and causes important environmental damage. Albuterol pMDIs have historically used the CFCs trichlorofluoromethane (CFC-11) and dichlorodifluoromethane (CFC-12) as propellants, both of which are potent ozone-depleting substances.

The production of ozone-depleting substances is being phased out under the terms of an international agreement called the Montreal Protocol on Substances that Deplete the Ozone Layer.<sup>17</sup> The Food and Drug Administration has announced a final rule to amend the regulation (21 Code of Federal Regulations 2.125) on the use of ozone-depleting substances in medical products. This rule establishes December 31, 2008, as the date by which production and sale of single-ingredient albuterol CFC pMDIs must stop and removes the essential-use designation for albuterol pMDIs.

Since most of the pMDIs available in the United States have contained CFCs, many of these are being reformulated. Several non-CFC products are currently approved and marketed for a range of different drugs, including non-CFC pMDI versions of albuterol, beclomethasone, fluticasone, and ipratropium, as well as dry powder versions of fluticasone, formoterol, and salmeterol. Other non-CFC products are in the latter stages of development.

Hydrofluoroalkane (HFA) pMDIs require a different metering valve, with a smaller aperture, which produces a much finer particle size with many medications.<sup>18,19</sup> As well, particle size is decreased for some corticosteroids (eg, beclomethasone and flunisolide) that dissolve into solution in HFA 134a but remain in suspension in CFC. No surfactant is used in the HFA devices, but alcohol is added for dispersal. It is probable that a change to HFA devices will require a reassessment of the age-related dose equivalence of CFC pMDIs, discussed later.

**Strengths.** The development of new environmentally friendly propellants presents an opportunity for major design enhancements of the pMDI. While some manufacturers of HFA pMDIs have focused on making the new de-

vices identical to their CFC predecessors, others have optimized the design to enhance aerosol delivery and canister/valve performance.<sup>19</sup>

Opportunities inherent in the new propellants and valves include a reduced tailing-off effect at the depletion of the canister's contents. With HFA pMDIs, when the end of canister life is reached, the emitted dose rapidly decreases to a negligible level. The HFA-propelled aerosol has a lower velocity and gentler plume, which, combined with smaller particle size, results in less oropharyngeal deposition.<sup>20</sup> These attributes make many of the new HFA propellant inhalers more reliable and efficient than their CFC predecessors.

**Limitations.** As a new device *and* a new carrier formulation, the HFA pMDI must meet more complex regulatory requirements for a new drug application. In the United States, HFA pMDIs are currently limited to only a few formulations. As well, the costs of manufacturing and development are substantially higher with HFA systems.

### Breath-Activated pMDIs

Pirbuterol (Maxair, 3M, St Paul Minnesota) and albuterol HFA (IVAX Laboratories, Miami, Florida) are available in the Autohaler in North America. In Europe they also have the Easyhaler breath-actuated device (Baker Norton, Ireland). These devices have a mechanical flow trigger that activates the device when inhalation flow reaches  $\geq 30$  L/min, which decreases the need for coordination.<sup>21</sup> They also produce softer mist. Because of the flow needed to activate these devices, patient ability to use the device is age-dependent.<sup>22</sup>

### pMDI Accessory Devices

Effective deposition of aerosols from pMDIs requires a fairly low inspiratory flow, a deep inhalation, and a breath-hold. Children gain skills as they grow older, and as these skills evolve, their breathing pattern and ability to effectively use an aerosol device change.<sup>11,23</sup> Airway deposition can be increased and mouth deposition can be reduced by accessory devices.

### Spacers

A spacer device adds additional volume to capture aerosol from a pMDI, but requires coordination of actuation with inhalation. Spacers all decrease oral deposition but provide limited protection against poor hand-breath coordination. Spacer size and shape can influence particle characteristics. Spacers are sometimes made from household items such as toilet paper rolls<sup>24</sup> or plastic soda bottles.<sup>25</sup>

## Valved Holding Chambers

A valved holding chamber is a spacer device that contains a one-way, low-resistance valve that allows the aerosol to remain within the device until the patient's inhalation effort opens the valve. Thus, the device can be considered partially breath-actuated. Valved holding chambers improve coordination with inspiratory flow, reduce the overall size of the aerosol particles (because larger particles impact on chamber walls), and eliminate the cold-Freon effect.<sup>26</sup> Some valved holding chambers have one-way exhalation valves to increase patient comfort and decrease rebreathing with masks, when these are left on the face during tidal breathing. Although the holding chamber design allows some delay, the aerosol should be inhaled very soon after the pMDI is discharged into the chamber, and only a single actuation should be discharged into the chamber for each inhalation.<sup>27–31</sup>

Valved holding chamber designs may need to be modified for the new HFA pMDIs. For example, it appears that some HFA formulations produce a slower particle velocity, smaller particle size, and a higher aerosol temperature. These changes will affect the quality of the aerosol spray.<sup>19</sup>

### Factors That Influence Effective Use of pMDIs

#### Valved Holding Chamber Inhalation Delay and Electrostatic Charge

Electrostatic charge in a plastic holding chamber can reduce the output of larger particles.<sup>28–35</sup> Electrostatic charge can be reduced by priming the chamber with the desired aerosol or by washing the chamber with ionic detergent and then air drying it.<sup>28–30,33–36</sup> Removing electrostatic charge by coating the spacer with a detergent layer can increase lung deposition by up to 300%.<sup>32</sup> This increase in performance is important and likely to substantially improve therapy with some children, though it may increase the risk of steroid toxicity in others. For inhaled  $\beta$  agonists, for which dosage is much less critical and toxicity is a relatively minor issue, the delivery improvement from removing static may not be as important clinically.<sup>28</sup> Only one published study showed no negative influence of spacer charge on the clinical efficacy of a  $\beta$  agonist in children with asthma, but the albuterol dose administered was on the peak of the dose-response curve.<sup>37</sup>

To maximize drug delivery, single actuations should be used for inhalation.<sup>27–31</sup> In comparative studies of drugs and dosages it must be remembered that the amount of drug emitted by the device is not the same as that inhaled by the patient.

## Face Mask Comfort and Seal

Aerosol deposition is negligible to a distressed child. Crying involves a long exhalation followed by short and rapid inhalation, so it is no surprise that aerosol delivery is much less to a crying infant.<sup>38,39</sup> Indeed, the problem of the distressed infant is often compounded by poor mask seal and shortened treatment times, almost ensuring that no medication is delivered.

A close-fitting mask is essential for adequate deposition.<sup>40</sup> Not only will a loosely fitting mask increase medication loss and effective dead space, for a valved holding chamber the loss of an effective seal may prevent the child from developing sufficient flow to open the inhalation valve.

### Breathing Patterns and Age-Related Deposition

While the fetus has a fully defined conducting airway early in its development, the airway size changes dramatically in the first years of life. The breathing pattern, flow, and volumes also change with growth and development. Resting respiratory rate decreases and tidal volume ( $V_T$ ) increases with age. In the first years of life,  $V_T$  is approximately 7 mL/kg of ideal body weight. There is a 300% increase in  $V_T$  during the first year of life.

Compared to adults, information regarding inhaled particle mass, lung deposition, and regional distribution of aerosols is limited for neonates, infants, and young children. Aerosol delivery is often less efficient with that population. While less is known about delivered dose, it appears that in most cases adult doses of aerosolized bronchodilator have comparable safety and efficacy in children.

The proportion of the prescribed dose deposited on an inspiratory filter or in the lungs increases with age, but the increase appears to be appropriate for the increase in body size, as the serum level of an inhaled drug is similar in children of different size and age inhaling from a given device. Therefore, the dose of an inhaled agent delivered via a pMDI and static-reduced valved holding chamber probably does not need to be adjusted for age.<sup>41–43</sup> A single study suggested that the systemic availability of nebulized drugs in young children is half that of adults given the same nominal dose.<sup>44</sup> However, the drug studied was a nebulized budesonide solution, which is lipophilic and therefore is a suspension formulation rather than a solution. Delivery of budesonide solution via nebulizer is inefficient and this probably influenced these results.

The development of high-efficiency HFA-propellant pMDIs that generate extra-fine particles in the range of 1.0–1.3  $\mu$ m mass median aerodynamic diameter may dramatically change our understanding of age-related aerosol



deposition patterns, and these recommendations will probably need to be revised.

### Device Dead Space

Large accessory-device dead space decreases deposition, especially with the smallest children.  $V_T$  remains fairly constant throughout childhood, at about 7 mL/kg of ideal body weight for age and height. Thus, a 1-year-old child who weighs 10 kg would have a  $V_T$  of approximately 70 mL. With both the device and the physiologic dead space, it takes 3–5 tidal breaths for that infant to clear a holding chamber with a volume of 145 mL. Larger chambers would take longer to clear, allowing more of the aerosol to settle in the chamber because of gravity or electrostatic charge.<sup>45</sup> There is also the challenge of keeping the young child quiet and comfortable with a mask on the face for enough time to clear the chamber. However, at the higher  $V_T$  generated by older children, delivery can be increased from a larger chamber, reflecting the larger dose available.<sup>46</sup>

### Canister Temperature and Canister Shaking

The emitted dose is decreased when the pMDI canister is cold,<sup>15,16</sup> especially in colder climates during winter months.<sup>47</sup> The emitted dose is typically measured under standard ambient temperature conditions. However, when a CFC albuterol pMDI is used at 0°C, the output is < 50% of that emitted at 23°C. This is particularly problematic during winter, when an asthmatic patient who has cold-induced symptoms keeps an inhaler handy in an outer pocket of a heavy coat.

Canisters that contain drug in suspension must be shaken before use to resuspend the drug. Over the life of a CFC pMDI canister, if the canister is never shaken, the amount of drug delivered is one third less than if the canister is shaken before each actuation.<sup>14</sup> Very rapid actuations can reduce the dose delivered per actuation because the CFC propellant chills the valve; however, albuterol pMDIs can be actuated immediately after a 10-second breath-holding pause without affecting the dose delivered.<sup>16</sup> It is probable that HFA propellant pMDIs are less dependent on temperature, shaking, or actuation pause.<sup>18</sup>

### Matching the Canister to the Boot

It seems to be somewhat important to match the pMDI canister to the boot and to use the correct accessory device to optimize delivery. Changing devices can alter particle size and dynamics, although the optimal combination may depend on how studies are conducted.<sup>48–50</sup> However, if the canister valve does not sit securely in the boot, not only

will a substantial amount of medication be lost, but both the valve and the boot can be damaged.<sup>24</sup>

When considering optimizing delivery by trying to match specific devices to each inhaler, it is important to remember that changing devices for different drugs can be confusing for patients and that confusion and consequent misuse of devices can have far greater effect than any benefit from trying to match the pMDI to the best accessory device.<sup>9</sup> This problem can be compounded when patients take some of their medications via DPI, which requires fast inspiratory flow to deaggregate particles, but use a pMDI to take other medications, such as albuterol, which is not available in a DPI in North America.

### Washing the Boot

Although the clinical impact of failing to wash the device holder is unclear, this may have implications for patient satisfaction and medication delivery, particularly for the newer HFA devices with smaller valves.<sup>51</sup>

### Patient Education

Patient training is important for the proper use of aerosol devices. In a recent study, data were collected concerning treatment regimens, the ability of parents to use a device, and the acceptance of the devices. Even though physicians were aware of the purpose of the study, no explanation or training in administering the treatment was given to 47% of the parents by the prescribing pediatrician. Errors in using the devices and in administering therapy were much more common when training was not offered.<sup>52</sup> Inhalation instruction should be given repeatedly to maintain correct inhalation technique with asthmatic children.<sup>12</sup> To be most effective, educational materials should focus on the patient's knowledge and empowerment, but the educator must also ascertain that caregivers are able to read and understand written instructions.<sup>26</sup>

### Adherence, Compliance, and Contrivance

It has been conclusively shown that inhaled corticosteroids significantly reduce the risk of death from asthma and that the risk increases dramatically as adherence falls off. In a large cohort study from Saskatchewan, the asthma death rate decreased by 21% with each additional canister of inhaled corticosteroids used in the previous year.<sup>53</sup> The most important cause of asthma medications' failure to work is that the patient is not taking them properly or at all.<sup>13</sup>

Adherence can be poor even when patients know that adherence is being monitored during a study. Medication under-use occurred on 55% of study days in one study that monitored adherence by an electronic device attached to

the pMDI boot.<sup>54</sup> In another study, while 73% of the participants reported using their inhaler an average of 3 times daily, electronic monitoring data showed that only 15% of the participants actually used the inhaler an average of  $\geq 2.5$  times per day. Fourteen percent showed a pattern of inhaler-actuation of  $> 100$  actuations in the 3-hour interval before clinic, reflecting deliberate emptying (dumping) of inhalers in order to appear compliant.<sup>55</sup>

Even with a strong education program, adherence still falls off after the first week of therapy.<sup>56</sup> Although some of this is due to lack of understanding or poor technique, some patients will contrive to use their inhaler device incorrectly.<sup>57</sup> It appears that poor adherence and contrivance to misuse devices is strongly associated with failure of therapy and asthma severity.<sup>58</sup> Highlighting this problem, in a study of 24 patients with severe asthma, 68% who were adherent to using their inhaled corticosteroid on most days did not require oral corticosteroids for breakthrough wheezing, whereas 86% of nonadherent patients required oral corticosteroids for an asthma exacerbation.<sup>59</sup>

### Summary

pMDIs are under-used in the United States. One barrier to use is the clinicians' misconception related to pMDI effectiveness relative to small-volume nebulizers, especially among pediatricians. This is despite strong evidence from well-controlled pediatric studies that pMDI is equivalent or superior to jet nebulization.<sup>2</sup> Another barrier in the United States is reimbursement. It appears that many third-party payers will reimburse for a nebulizer/drug package but not for a pMDI and holding chamber. Educational efforts targeting clinicians, patients, reimbursement agencies, and regulators are needed to address these issues. We discuss reimbursement issues in greater detail in our companion paper from this conference.<sup>61</sup>

These issues will become all the more important as we look forward to the development of new delivery systems and the availability of novel drugs for aerosol delivery, such as systemic delivery of peptides and proteins via the airway.<sup>60</sup>

Finally, and most critically, no medication will work if it is not taken properly and consistently. No matter how efficient and "user-friendly" we make the delivery system, patients will not use what they do not like or do not understand. Sadly, some patients will not even use a medication and device that they understand and like. Our challenge is to help the patient to make this process as easy and as important as possible.

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## Discussion

**Geller:** Bruce, regarding the study you did on the force-versus-dead-space of masks on an infant face, has anybody done an in vivo study on how much force young children will tolerate on the face?

**Rubin:** Outstanding question. The first problem with using an infant mask is getting the infant to hold still to allow the repeated force application. Even with different masks it is nigh impossible. With a mannequin, we asked people to show us how they do this with their child, and we looked at what was done in practice.

**Lacke:**\* Do you use any of the "character" masks that are designed to improve compliance with children?

**Rubin:** No, I have not. There's one from Israel that looks like a toucan bird. We tend to use a mouthpiece with any child who is old enough to reliably sip from a straw. With 3-to-4-year-olds we start introducing the mouthpieces rather than the mask. For the younger ones, I'm not so sure the character masks make a difference as to whether the parents are going to take the time and make this part of the routine to do with their child. I think a lot of this is more parent-driven rather than driven by the child's interest in wearing a Mickey Mouse face.

**Smaldone:** We tried to jam masks against the face but still weren't able to prevent leaks, so there is a dead-space issue, but the only way to completely prevent leak would be to glue the mask on the kid's face. I talked to Johannes Wildhaber about this because I know he's done some deposition studies with kids.<sup>1</sup> I'm not sure how they did those studies, but he men-

tioned that they tried petroleum jelly around the mask to minimize leak.

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**Rubin:** We use masks when we do infant pulmonary function studies. We sedate them, put the mask on by hand, and measure. We assume that there is minimal leak, but I don't know if that has been tested. We did it by looking at charcoal distribution; if there was complete distribution from the mask, we assumed that at some time it was fairly comfortably seated.

**Fink:** In almost all of the mask studies I've seen, the infants look like white babies. Different races have different facial characteristics, such as shape of the bridge of the nose, which can impact mask fit. We need to look at the effect on mask sealing and leak with a wide array of patients.

**Rubin:** Very good point, even with us white babies genetically destined to have rather large protuberances. But the nose size is much smaller in infants and possibly more similar among Asian, black, and white children in the first year of life.

**Fink:** We found that a mask that had a pronounced nose bridge leaked like crazy when we used it with an Asian baby whose nose bridge was flat; we had to use a circle type mask to secure a fit. Mask characteristics could allow more aerosol to leak towards the eyes with some infants.

**Nikander:**<sup>†</sup> Regarding "one-size fits all," it has been shown that a stainless-steel valved holding chamber de-

livered the same dose of budesonide to young children and adults, but the plasma concentration was similar. This meant that lung deposition increased with age.<sup>1</sup> The particle size of the budesonide MDI was probably about 3  $\mu\text{m}$ . This supports the claim of "one size fits all." The question is whether the new HFA formulations, which create particles of about 1  $\mu\text{m}$ , will behave similarly with a valved holding chamber.

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**Rubin:** I can't answer that question, but regarding effectiveness, considering that we're on the low end of the dosage scale and we recommend a huge margin of safety with inhaled corticosteroids, if you stick to that end, you're okay. But I don't see why the airway epithelium of a small child with asthma would be more sensitive to inhaled corticosteroids or that you would get better corticosteroid effect than with an asthmatic adult.

**Geller:** I think the clinician should adjust the dose downward, based on clinical effect, to use the minimum effective dose. You have to use the dose that works clinically, and whether that's the same as or less than the adult dose depends on the child, the disease, and the situation. So that's a clinical decision, not an in vitro "guessimate."

**Fink:** When I took the National Board for Respiratory Care's neonatal-pediatric exam, there were at least 6 questions on cutting the terbutaline dose to infinitesimal amounts based on body weight. If I understand your presentation, you're basically saying that the actual amount per kilogram that an adult gets with an adult dose and an infant gets with an adult dose is the same. Our problem is that we

\* Steve Lacke, Cardinal Health, McGaw Park, Illinois.

† Kurt Nikander, Respironics, Cedar Grove, New Jersey.



have no data on what dose is really appropriate for infants, because those studies haven't been done.

**Hess:** What is the minimum amount of time that we need to wait between actuations from an MDI?

**Rubin:** If you wait for the MDI canister to warm, then you're probably talking about 15–20 seconds. With an HFA inhaler, virtually no time is necessary if you're waiting for it to warm and redistribute.

**Newman:** A few years ago, for CFC inhalers we recommended that there should be at least 30 seconds between doses. I don't think anybody has ever proved that an interval as long as 30 seconds is really necessary.

**Fink:** In 1996, Rajiv Dhand and I reported a bench study of MDIs in the ventilator circuit, in which we tried to determine the difference in aerosol output between shaking between every actuation for 8 puffs, and shaking once before 8 puffs, and between actuations every 1 minute and actuations every 15 seconds.<sup>1</sup> We found that if we shook once and left it in the adapter, we got more drug on the subsequent actuations, up to 8 puffs. We also found that firing at 15-second intervals was as effective as 30-second intervals, up to the total of 8 puffs.

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**Hess:** What if you shook it and actuated it every 5 seconds? I have seen respiratory therapists do that into the ventilator circuit.

**Fink:** We started to get a reduction in output when we actuated with intervals less than about 15 seconds.

**Leach:** With the HFA devices it's not really the device that's limiting things, it's the patient, especially if you want the patient to breath-hold. We researched that because we were performing radiolabeled beclomethasone lung deposition studies using SPECT, and we needed to get the inhaled dose high and into the patient as fast as possible. With healthy subjects we optimized on one inhaled dose every 20 seconds. That included a 10-second breath hold.

**Hess:** But that may be different in a mechanically ventilated patient.

**Dhand:** I think that drug doses could decrease if an MDI is actuated too rapidly in succession. It requires some time for the pressure in the MDI to equilibrate; that is very important for its operation. Although there are no studies on this issue, to the best of my knowledge, there may also be differences in the amount of exhaled aerosol when the MDI is actuated with a breath every 5 seconds.

**Rau:** There was some data from Mark Everard<sup>1</sup> on this delay question—not about the patient effects but about what comes out from the nozzle, the amount of drug and characteristics. Basically, the finding, as I recall, was that if you fire twice within a couple of seconds, there's no real difference in total mass emitted, nor fine-particle fraction. But once you got beyond firing twice in a row, then you began to see a drop in fine-particle mass. So even if it was within 10–15 seconds, if you fired it 3 or 4 times, then the fine-particle mass decreased. So, practically speaking, it made no difference with 2 actuations; if you fired 2 actuations very quickly, there was no important difference. But once you get to 3 or more you begin to see differences, which are probably due to what Rajiv mentioned, the filling characteristics of the delay time with self-metering valves.

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**Hess:** Joe [Rau], don't you have some data that suggest that it is not good to do rapid multiple actuations into a spacer?<sup>1</sup>

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**Rau:** I think you reviewed that paper, about which *Chest* gave us some good feedback, which was that as you start firing multiple times into a chamber, the amount of emitted dose decreases—somewhat similar to the data that you showed. I think O'Callaghan's findings were similar.<sup>1</sup> We fired up to 3 puffs into a chamber. We fired 2 seconds apart, and the amount of emitted dose on inhalation from the chamber per firing goes down, very linearly, at least up to 3 actuations.

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**Fink:** I have an anecdotal observation. When administering pMDIs to mechanically ventilated adult patients, 15-second intervals gave us a puff every third breath. When we would administer puffs every 1 or 2 breaths, the patients had more coughing and apparent irritation than with actuations every 3 breaths.

**Amato:**<sup>‡</sup> There is a peer-reviewed study by Clark et al<sup>1</sup> on multiple ac-

<sup>‡</sup> Michael T Amato, American Respiratory Care Foundation, Irving, Texas; Monaghan Medical/Trudell Medical International, Syracuse, New York.

tuations into a chamber, and it also found that the subsequent actuations were almost totally lost in the chamber.

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**Rau:** That's different, because you're not talking about how many actuations you can fire into some type of chamber and then get a normal or nominal dose out. You're bringing in a time delay, which affects what comes out of the chamber.

**Atkins:** Everything that we just talked about will be different for different products, for different drugs, or for albuterol inhalers from different manufacturers. I would caution that some of these things that have been stated as fact need to be studied, as they may not apply universally. There are big differences between the be-

haviors of, for example, suspension and solution MDIs, and between CFC and HFA MDIs.

**Ahrens:** I want to address the issue of patient adherence to treatment plan. You talked about how poor adherence may be a particular problem with some of the devices and treatment plans. This makes me wonder why patients don't actually use these treatments. I suspect that it's not often because they've actively decided not to take the medication, or because they don't like the device, but because they simply don't remember to do it. Anecdotally, it seems the only way for many patients to overcome this is to put their daily medication on top of their toothbrush or somewhere else where they'll be reminded during their normal activities of daily living. Have you looked at the adherence literature enough to know if there are any take-home messages or general teaching tools clinicians can use to promote adherence?

**Rubin:** My overall perspective on the adherence literature is that if you

make it really important to the patient, and easy to do, they'll do it. Toothbrushing is a good reminder. People may forget to take their statins, but they certainly don't forget to take medications when it's important to them. If you are suffering from a headache, you'll remember to take the medication. If there are immediate consequences, they'll remember. Patients with cystic fibrosis remember to take their pancreatic enzymes, because they know the consequences if they don't. They'll often forget to take the other medications and they'll certainly not do their chest physical therapy, because they don't see the immediate consequences. For some parents and children the importance isn't clearly immediate. We need to make taking medication important for patients and their parents, and to make it as easy as we can, which includes making the drugs easy and reliable to obtain, and inexpensive. We also must teach and re-teach the techniques, and when patients come back, we should evaluate that they are using the devices properly.