

Improper patient techniques with metered dose inhalers: Clinical consequences and solutions to misuse

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The use of inhaled medications for the treatment of lung diseases has been part of the pharmaceutical armamentaria of health care providers for millennia. Two thousand years before the onset of the Christian Era, tribal Shaman of the Indus Valley used "smokes and fumes" from burning roots (*datura*, a congener of *atropine*) to treat cough and wheezing.^{1,2} As contact between centers of civilization expanded, the use of inhaled vapors for medicinal and psychosocial purposes became widespread in the ancient world, and the technology for aerosol delivery evolved from kettles and hot pots to the development of various types of pipes.^{1,3}

However, with the rise of Christianity as the official religion of the Roman Empire, the ways of the past were suppressed. In their zeal to make a new beginning for mankind, the traditions and beliefs (both good and bad) of the "pagans" were repudiated by the early Christians, and the teachings and therapies of the ancients were held suspect. The Dark Ages sealed this position, and as intellectualism stagnated in the West, former modes of therapy were lost. During this period the development of inhalational medicine continued mainly in the East. As the Renaissance brought current civilization into intellectual contact with the past, art, philosophy, and science flourished, and social and commercial pressures served as the impetus to repair the neglect of centuries. Progress, however, was slow and uneven, particularly in medicine. By the onset of the nineteenth century, Europeans had again recognized the value of inhalants and began to embrace their use enthusiastically.

The first atomizer was invented in 1849.¹ Hand-held nebulizers followed in the twentieth century,

Abbreviations used

FEV₁: Forced expiratory volume in 1 second
MDI: Metered-dose inhaler

and one of the earliest reports that used an inhaled sympathomimetic for the treatment of airway obstruction was in 1935.⁴⁻⁶ Twenty years later, pressurized metered-dose inhalers (MDIs) made their appearance.⁷ The convenience and efficacy of these devices soon materially altered treatment patterns, and currently hundreds of millions of MDIs are prescribed yearly.

Unfortunately, as with other aspects of human existence, technologic advances have begotten their own problems. Although there is no question that MDIs provide more precise drug delivery profiles and are infinitely less cumbersome to use than hand-held or compressor-driven nebulizers, patient interactions with the devices are not always optimal. The purpose here is to explore the advantages and disadvantages of MDI therapy and to evaluate the efficacy of potential solutions.

CLINICAL ADVANTAGES OF MDIs AND AEROSOL PHARMACODYNAMICS

Virtually any type of drug that can be put into stable suspension or powder can be used as an inhalant. Currently MDIs that contain a number of different β -agonists and glucocorticoids are commercially available, as are preparations with anticholinergics and antiinflammatory agents such as cromolyn sodium and nedocromil. The major advantages of aerosol therapy are the direct delivery of medication to the site of need, a rapid onset of action, and the small quantities of drug required to produce a beneficial effect. The respiratory tract has an enormous surface area, and active and passive transport mechanisms facilitate absorption from the epithelial surface to the tissues of the tracheobronchial tree. Thus this route of therapy is quite effective, particularly in the treatment of

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airway diseases. With β -agonists and glucocorticoids, the dose of medications required to produce a meaningful clinical response is at least 10 and sometimes more than 20 times less than the amount needed to induce comparable improvements by other routes of delivery. Consequently, MDIs produce less systemic side effects. This aspect of inhalation therapy has proved to be particularly beneficial in the case of inhaled steroids.

In addition to the above, the portability and compactness of MDIs make them ideal for ambulatory therapy. The quantity of medication is aerosolized in accurate and reproducible doses, and the amount of bronchodilatation that occurs with a given β -agonist in an MDI is equal to that seen with a jet nebulizer and occurs within minutes.^{8,9} Furthermore, there is a growing trend for MDIs to replace conventional nebulized bronchodilators in the treatment of acute airway obstruction in emergency rooms or hospitalized patients.¹⁰⁻¹² In these circumstances the MDIs are usually administered by a health care provider rather than the patient and a spacing device is incorporated. Because the time required by the therapist to provide aerosol treatment at the patient's bedside can be dramatically reduced with this approach, major cost savings can result.¹²

Unlike the situation with the jet nebulizer compressor system, the output from an MDI is not a steady stream of particles but rather a bolus of aerosol that lasts perhaps 100 msec.¹³ During this time, particle size and velocity are constantly changing. The leading edge of the aerosol cloud expands as the particles encounter resistance, and within a few centimeters of the exit port of the MDI, the bolus becomes pear shaped. Therapeutic aerosols are deposited in the respiratory tract primarily by either inertial impaction or gravitational sedimentation. The former tends to occur whenever the airstream changes direction abruptly or encounters obstruction and is greatly enhanced by either increasing airflow velocity or particle size or both. Particles with a mass median diameter between 1 and 5 μm can penetrate into the lung and be deposited onto the airways.¹⁴ Those larger than this tend to impact in the upper airway, whereas those smaller are exhaled with the next breath and lost. To achieve a therapeutic benefit, the patient needs to inhale as much drug as possible in the appropriate size range and distribute it throughout the airways before the cloud develops unfavorable aerodynamic properties or dissipates entirely. Even under the best of circum-

stances this is a difficult feat, and it is estimated that only 10% of the drug released from an MDI ever reaches the intrathoracic airways.¹⁵ The remainder is deposited in the actuator, the mouth, and the oropharynx.

Aerosol deposition and the resulting therapeutic response are critically dependent on the patient's inhalation technique.¹⁴ As expected, the most important variables are the absolute volume of air inhaled, the inspiratory flow rate, and the duration of the end-expiratory breath hold.¹⁴ Most patients tend to inhale rapidly from an MDI unless instructed otherwise. Unfortunately, the faster the inspiration and the smaller the volume, the greater the deposition in the oropharynx. In contrast, the larger the volume inhaled and the slower the rate, the greater the quantity of drug that penetrates into the lungs. Breath holding also increases deposition by permitting more time for the particles to settle. The optimum duration of apnea appears to be around 10 seconds.¹⁶ In one study with low inspiratory flow rates, greater bronchodilatation was found with a 10-second rather than a 4-second pause. Extending the apnea to 20 seconds offered no additional improvements.¹⁶

The lung volume at which inhalation starts and the position of the inhaler relative to the mouth may influence bronchodilator response, but the effect is not as marked as that seen with the factors mentioned previously. It has been argued that inhalation from functional residual capacity is more efficacious than that from residual volume,^{17,18} but this probably is not an important variable.¹⁹ With respect to inhaler position, it is often recommended that the MDI be held several centimeters from the open mouth^{20,21}; however, direct comparisons between this technique and that where the lips are closed about the mouthpiece have not shown uniform differences.^{16,22,23}

DISADVANTAGES OF MDIs

There are several disadvantages to the use of MDIs. The first is environmental. The current pressurized devices contain chlorofluorocarbons as propellants, and the release of such agents into the atmosphere contributes to ozone depletion. This effect is quite small (<0.1%) in comparison with other sources of chlorofluorocarbons but is mandated by outside forces to be eliminated totally in the near future when these particular compounds are phased out of production by international treaty and replaced with non-ozone-depleting alternative propellants. The major problem with MDIs is that they are difficult for some patients to use, and because faulty technique leads to subop-

timal therapeutic responses,^{24, 25} poor control of the airway disease ensues.

Patient errors in the use of MDIs began to be observed shortly after the devices were introduced into clinical practice, and unfortunately continue to remain a serious issue. From the original description of the phenomenon in 1965²⁶ to the present, 20 articles are available for review in the English language literature.^{24, 27-44} Because this experience involves more than 3600 patients, it provides a considerable database to examine the salient features of the problem. The number of subjects who could not use inhalers correctly has varied from a low of 12%³⁴ to a high of 89%³¹ of the populations examined. The average incidence of misuse for the entire series is 38% (1308 of 3611 persons had one or more deficiencies in technique).

Incompetence with inhalers has been found in all age groups but particularly in the young and the elderly.^{36, 38-40, 44} There does not appear to be any gender predilection. In some studies naive subjects and those who have taught themselves from reading printed directions use MDIs less effectively than those with previous experience or who have received instructions.^{32, 34, 37, 41} However, significant numbers of individuals in the latter two groups do not demonstrate optimal technique with MDIs either.^{28, 34, 38, 41}

Twelve of the above-referenced studies contain sufficient detail to permit a catalog of the mistakes that the subjects made.^{24, 29, 31, 33, 34, 36-40, 42, 44} Nine hundred fifty-five people committed 1536 errors. The principal types, in decreasing order of frequency, were failure to coordinate actuation of the MDI on inhalation; that is, hand-lung discoordination²⁹ (27% of recorded problems^{29, 31, 33, 34, 36-40, 44}); too short a period of breath holding after inhalation (26%^{24, 31, 37-40, 42}); inappropriately rapid inspiratory flow rates (19%^{24, 31, 38, 40, 42}); and an inadequate shaking and mixing of the contents of the inhaler before use (13%^{31, 37, 38, 42}). The last is obviously the least significant. Much less common but equally consequential are events such as an abrupt discontinuation of inspiration as the aerosol cloud strikes the back of the throat (the so-called "cold freon effect").³⁴ This phenomenon occurred in 6% of the population.^{34, 38, 39} Actuation of the MDI at total lung capacity was seen in 4%^{33, 34, 36, 39} and firing of the MDI in the mouth but inhaling through the nose was observed in 2%.^{33, 34, 39} A few persons exhaled during activation,^{33, 34} put the wrong end of the inhaler in their mouth,³⁹ or held the canister in the wrong position.³¹ Four partici-

pants failed to take the cap off before use,^{31, 39} and 3% fired the inhaler multiple times during a single inhalation.^{31, 34}

The hand-lung discoordination problem can take several forms. Individuals will either release the medication too early or too late in the inspiratory pattern so that the aerosol cloud is not carried into the lung efficiently. The extreme variations on this theme are actuation of the MDI without inspiration or inspiration without actuation.^{29, 34} All these patterns, particularly the latter, tend to occur with increased frequency in the frail and elderly.^{39, 40} Competence with an MDI in the elderly is not a function of age or underlying diagnosis³⁹ but rather seems to be related to the hand strength and finger dexterity needed to fire the inhaler.⁴⁰ Even using a two-handed approach, some elderly patients do not have the power to depress the canister of an MDI into its socket with sufficient force to release the contents.

The reasons underlying poor patient performance with MDIs are multiple. Besides physical limitations, a significant cause of patient incompetence revolves around the instructions they are given. Of critical concern is the fact that many patients either do not receive any formal training in the proper use of MDIs from health care providers or are taught by persons with limited knowledge of the devices being demonstrated.^{28, 29, 34, 45, 46} When left on their own, many patients cannot master the techniques necessary to inhale aerosols effectively by reading the instructions that accompany the canisters.^{28, 29, 34} Typically neither the patient nor the physician will be aware of the inability until the patient is asked to demonstrate his or her technique with the device. Consequently, the patients' airway disease is not optimally controlled even though they are complying with their medications. More disturbing is the fact that several investigators have demonstrated that a large percentage of physicians, nurses, and pharmacists do not know how to assemble or use MDIs correctly.^{45, 46} Respiratory therapists are much better than the other groups, but here too errors can be found.⁴⁶ Thus not only do patients need to be instructed in the proper technique but so do the medical staff who teach them.

The best means of instruction is open to debate. Verbal instructions and verbal instructions with visual feedbacks have been evaluated.⁴¹ Both have been found to be equally effective in converting incorrect to correct users; however, verbal instructions alone require less time. It is important to appreciate that regardless of the method used,

recidivism is high. It is estimated that after training, 50% of people with poor technique return to their old habits or develop new errors with the passage of time^{34, 41} and that as many as 15% of individuals will be unable to use inhalers despite adequate tuition.^{29, 34} Furthermore, follow-up studies have shown that as many as 20% of individuals who are competent with MDIs on one occasion may show problems with their use at a later date.⁴¹ Patients who demonstrate good or proper technique may be inconsistent in using this technique, especially during an acute attack. Occasional users are more prone to technique error than regular users. Hence periodic examination of inhaler technique is mandatory so that errors can be corrected and appropriate use reinforced.

CONSEQUENCES OF FAULTY INHALER TECHNIQUE

The obvious consequences of faulty technique are a reduction in the amount of medications delivered to the intrathoracic airways. The easiest way to assess the magnitude of this phenomenon clinically is by measuring the amount of bronchodilatation that occurs with an aerosolized sympathomimetic during controlled and spontaneous inhalations. In one small trial the difference in the mean response in the improvement in forced expiratory volume in 1 second (FEV₁) after two puffs of drug between efficient and non-efficient users approached 50%.²⁴ In the former group controlled inhalation did not significantly change pulmonary mechanics compared with the spontaneous use of the MDIs, whereas in the latter, controlled inhalation produced an additional 30% increase in FEV₁. These findings clearly demonstrate that limited bronchodilatation follows inadequate use. In addition to the physiologic sequences of MDI misuse, there are economic impacts as well. One study in a hospital-based population has suggested that as much as \$900 per month was wasted on the purchase of inhalers by 23 patients who could not operate them effectively.⁴⁷

SOLUTIONS TO MISUSE: INHALATION AIDS FOR MDIs AND NEW INHALATION DEVICES

To overcome the problems with coordination and to enhance aerosol deposition in the lower airways, a number of inhalational aids have been added to conventional MDIs, and different types of inhalers have been developed. The inhalational aids are collectively known as "spacers" and fall into three categories: (1) tubes without valves, (2) tubes or reservoirs with valves, and (3) collapsible

bags.^{14, 48, 49} The purpose of spacers is to slow down the aerosol spray before it reaches the mouth, thus allowing propellants time to evaporate and large particles to settle out of the cloud. In this fashion less deposition occurs in the oropharynx and more in the intrathoracic airways.¹⁴ Spacers can also overcome the need for synchronization between firing the aerosols and inhaling.¹⁴ Large volume spacers and tubes with valves are particularly useful in this regard. However, their bulk frequently makes patients reluctant to carry such devices with them or to use them in public.

How effective are these aids? Most would agree that spacers decrease oropharyngeal deposition and their use with steroid aerosols, particularly when the latter are given in high doses, and helps limit local side effects such as thrush and dysphonia. In terms of bronchodilatation, however, the literature contains mixed results. Some studies indicate that spacers confer an enhanced bronchodilator response,^{49, 52} whereas others do not find this result.⁵³⁻⁵⁷ Part of the confusion stems from the fact that if a given person is using an MDI well, spacers do not add any additional benefit.⁵¹⁻⁵⁷ If someone is using the MDI ineffectively, however, spacers may make the difference between a good and a poor therapeutic effect. The issue is seldom black and white, and in most cases spacers only moderately enhance the magnitude of bronchodilation.

Other solutions have been the development of breath-actuated, nonpressurized dry powder aerosols such as the Spinhaler, Rotahaler, Diskhaler, and Turbuhaler.⁵⁸ All these instruments are as effective as conventional MDIs, but the first three require higher quantities of drug to achieve the same effect. They do not have the problems associated with propellants and coordination as do MDIs, but drug delivery is dependent on the patient's inspiratory effort. The Spinhaler and Rotahaler are single-dose devices; for some patients loading them is problematic. The Turbuhaler and Diskhaler contain 200 and eight doses, respectively, to overcome this problem.

Most recently a breath-actuated, pressurized MDI has been introduced. As the patient inhales, a valve is actuated when a critical inspiratory flow rate is reached. The device is easy to use,⁵⁹ even for patients with severe impairments and markedly reduced inspiratory flow rates.⁶⁰ Like the dry powder inhalers, this device eliminates problems of coordination of inhalation and activating the canister and provides an alternative to the need for spacers. Direct comparison of this inhaler with

conventional MDIs in patients with poor technique shows encouraging results. As with spacers, those persons who coordinate activation and inhalation had similar degrees of deposition of aerosol in their lungs as well as equivalent bronchodilatation.²⁵ In contrast, in those persons who could not use their conventional inhalers appropriately, the percentage of the dose of medication deposited in their lungs was three times higher with the breath-actuated system, and the degree of bronchodilatation followed suit.²⁵

In summary, the availability of means of reliably delivering effective quantities of aerosol medication to the site of need in the respiratory tract has greatly facilitated the care of patients with airway disease. MDIs have become a standard form of therapy, and it is expected that even greater reliance will be placed on these devices as the emphasis on treating the underlying inflammatory components of these diseases gains momentum. Growing awareness of the patient's difficulties with coordination has led to further development of MDIs, such as the addition of spacers, or more recently breath-actuated devices. Other alternatives now include dry powder devices. In the near future when chlorofluorocarbons can no longer be used as propellants, we should see the development of non-ozone-depleting alternative propellants for MDIs and improved dry powder delivery systems.

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