The Inhalation of Drugs: Advantages and Problems

Joseph L Rau PhD RRT FAARC

Inhalation is a very old method of drug delivery, and in the 20th century it became a mainstay of respiratory care, known as aerosol therapy. Use of inhaled epinephrine for relief of asthma was reported as early as 1929, in England. An early version of a dry powder inhaler (DPI) was the Aerohalor, used to administer penicillin dust to treat respiratory infections. In the 1950s, the Wright nebulizer was the precursor of the modern hand-held jet-venturi nebulizer. In 1956, the first metered-dose inhaler (MDI) was approved for clinical use, followed by the SpinHaler DPI for cromolyn sodium in 1971. The scientific basis for aerosol therapy developed relatively late, following the 1974 Sugarloaf Conference on the scientific basis of respiratory therapy. Early data on the drug-delivery efficiency of the common aerosol delivery devices (MDI, DPI, and nebulizer) showed lung deposition of approximately 10–15% of the total, nominal dose. Despite problems with low lung deposition with all of the early devices, evidence accumulated that supported the advantages of the inhalation route over other drug-administration routes. Inhaled drugs are localized to the target organ, which generally allows for a lower dose than is necessary with systemic delivery (oral or injection), and thus fewer and less severe adverse effects. The 3 types of aerosol device (MDI, DPI, and nebulizer) can be clinically equivalent. It may be necessary to increase the number of MDI puffs to achieve results equivalent to the larger nominal dose from a nebulizer. Design and lung-deposition improvement of MDIs, DPIs, and nebulizers are exemplified by the new hydrofluoroalkane-propelled MDI formulation of beclomethasone, the metered-dose liquid-spray Respimat, and the DPI system of the Spiros. Differences among aerosol delivery devices create challenges to patient use and caregiver instruction. Potential improvements in aerosol delivery include better standardization of function and patient use, greater reliability, and reduction of drug loss. *Key words: aerosol, metered-dose inhaler, dry powder inhaler, nebulizer, MDI, DPI.* [Respir Care 2005;50(3):367–382. © 2005 Daedalus Enterprises]

Introduction: The Inhalation of Drugs for Respiratory Disease

The use of inhaled and aerosolized medications for treatment of diseases of the respiratory tract has a long history in medical therapy. Inhalation therapy for asthma and other complaints had a traditional place in Ayurvedic medicine, whose origins date back 4,000 years.[1] In 17th-century Ayurvedic literature there are instructions for smoking an anticholinergic preparation from the Datura group of herbs for asthma or cough with dyspnea.[1] Inhaled Datura for asthma was recorded in 1802 in Britain, and in 1797 a Philadelphia physician, Samuel Cooper, experimented with Datura stramonium preparations.[1] Asthma cigarettes (Fig. 1) (which contained stramonium leaves and had atropine-like effects), along with powders and cigars, were widely used in the 19th century as "fuming asthma remedies."[1,2] Medications have also been added to boiling water to allow inhalation.

Muers reports that the word "nebuliser" was defined in 1874 as "an instrument for converting a liquid into a fine spray, especially for medical purposes."[3] Seeger's fire-powered steam nebulizer was advertised in Geo. Tiemann

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Fig. 1. Methods of inhaling formulations of stramonium, an atropine-like compound with anticholinergic effects, used in the 19th century.

and Co's Surgical Instruments Catalogue in New York in 1876.[3] After the turn of the 20th century, newly discovered and isolated preparations of epinephrine and ephedrine began to supplant use of atropine-like substances such as stramonium.[1]

Origins of Modern Aerosol Therapy

In 1929, in England, Camps evaluated and recommended use of epinephrine via inhalation, and described "spraying it into the tracheobronchial tract."[4] In a 1948 publication, Benson and Perlman described the "spray method for administering epinephrine" as originating "with certain relatively obscure individuals in the Pacific Northwest" of the United States.[5] They state that these individuals "appear not to have contributed to the regular medical journals, but have formed companies to produce a racemic brand of epinephrine and a fine nebulizer for administration."

Benson and Perlman[5] kept a record of 2,236 asthma patients in their practice, and reported that 48 of 648 users of oral spray epinephrine were fatalities (7.4%), while only 22 of 1,588 non-users were fatalities (1.4%). Although not acknowledged by those authors, their results were early evidence that inhaled β agonists alone will not control the sometimes fatal pulmonary inflammation of asthma. Their work presaged the subsequent debate over the potentially harmful effects of inhaled β_2 agonists in asthma almost 50 years later.[6] The kit sold for inhaling epinephrine consisted of a bottle of 1:50 solution of racemic epinephrine and an all-glass nebulizer, which in all likelihood was the DeVilbiss No. 40 glass nebulizer (Fig. 2A), introduced for treatment of asthma in the 1930s.[3,5]

The first real precursor to the modern T-piece plastic hand-held pneumatic nebulizer was the 1950s Wright nebulizer (see Fig. 2B), made of Perspex, a shatter-resistant plastic used for fighter-plane canopies.[3] This device used a combination of gas flow, precise venturi orifices, and baffles to produce aerosol particles more in the fine particle range of 1–5 μm. The earlier DeVilbiss glass nebulizer and hand-bulb atomizers generated a wide range of particle sizes, and many of the particles were too large to reach the lower airways.[3]

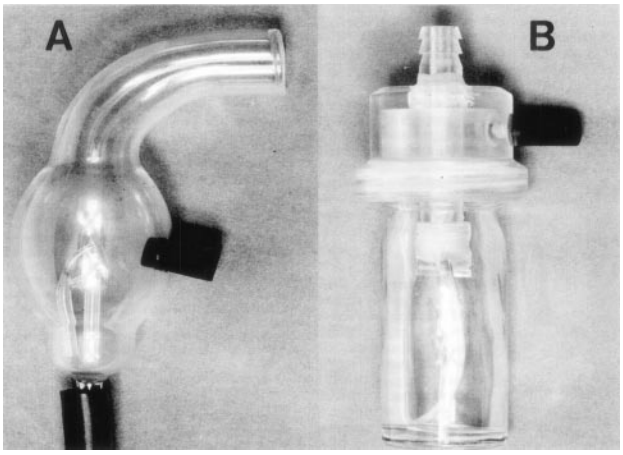

Fig. 2. A: The DeVilbiss No. 40 glass squeeze-bulb nebulizer. B: The Wright jet-venturi nebulizer, introduced in the late 1950s.

In 1944, Bryson et al published work on the introduction of nebulized penicillin for treatment of respiratory infection.[7] They described a mist formed by oxygen or air forced through aqueous solutions of the drug. Shortly thereafter, in 1949, Krasno and Rhoads described the inhalation of penicillin dust for management of respiratory infections, particularly sinusitis.[8] Their inhalation device, known as the Aerohalor (Fig. 3), was produced by Abbott Laboratories. This was actually the first dry powder inhaler (DPI), and it used small cartridges of powdered penicillin

Fig. 3. The Aerohalor was an early dry powder inhaler, reported by Krasno and Rhoads,[8] used for inhalation of penicillin dust to treat respiratory infections. (From Reference 2, with permission.)

that fit into a rather modern-appearing clear plastic inhaler.[2,8] The advantages of aerosol drug delivery noted by Krasno and Rhoads remain those seen with aerosol therapy today: simplicity, low cost, little need for manipulation or instruction, no pain of injection, sustained localized action, and less local irritation than liquid nebulized penicillin.[8]

Development of Modern Aerosol Delivery Devices

One of the most interesting stories of drug-device implementation is the origin of the metered-dose inhaler (MDI), as described by Charles G Thiel.[9] Thiel worked for Riker Laboratories, a subsidiary of Rexall Drugs and the company that developed the MDI. In 1955, Susie, a 13-year-old asthmatic, struggled with her squeeze-bulb nebulizer, and asked her father why she couldn't get her inhaled medicine from a spray can, in the way in which hairspray is packaged. Susie was the daughter of George Maison, then President of Riker Laboratories. Apparently her father had also been frustrated with the fragile, easily breakable glass-bulb nebulizers. In the spring of 1955, a propellant ("FREON," a trademark name for a certain mixture of chlorofluorocarbons 12 and 114), a metering valve, a glass vial device, and drug formulations of isoproterenol and epinephrine were investigated and assembled. In June of 1955, a clinical trial was conducted at the Long Beach, California, Veterans Administration Hospital by a Dr Karr.

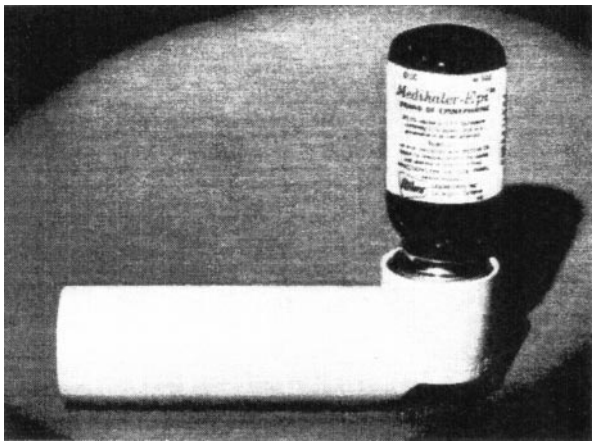

Fig. 4. The Medihaler-Epi was the original metered-dose inhaler for epinephrine. (From Reference 9, with permission.)

The New Drug Application was filed on January 12, 1956, and consisted of a file only 13 mm thick—unheard of in today's new-drug-submission-and-testing system. The drug-delivery device was approved by the Food and Drug Administration on March 9, 1956, and the Medihaler-Iso and the Medihaler-Epi were launched later that month. It is even more interesting that the original MDI of Medihaler-Epi (Fig. 4) differs very little from the appearance and even function of current MDI devices. Following the release of the MDI, a DPI (the SpinHaler) for delivery of the anti-asthmatic drug cromolyn sodium was developed and approved. The article by Bell et al,[10] describing and evaluating the SpinHaler, gave the following rationale for the new device:

> It is not generally realized that, with the pressurized aerosol. . . the administration of medication requires coordination of activation with the inspiratory cycle of respiration if variation in the quantity and site of drug deposition in the airways is to be minimized.[10]

Bell et al[10] noted a primary problem for optimal use of MDIs, namely, the difficulty for patients in activating the MDI while simultaneously beginning a slow deep inhalation. Because it was a breath-actuated device, the SpinHaler relied on the force of a patient's inspiratory flow to spin a small plastic propeller, thereby creating turbulent airflow through the device, and disaggregating drug powder from its carrier lactose particles (Fig. 5),[11] which created a fine powder suitable for penetration to the lower airways. The SpinHaler was breath-actuated, so it eliminated the need to coordinate device actuation with patient inhalation (which is critical to effective MDI use).

The problem of coordinating inhalation with MDI-actuation, along with the high loss of drug in the oropharynx, which contributes to systemic adverse effects, ultimately

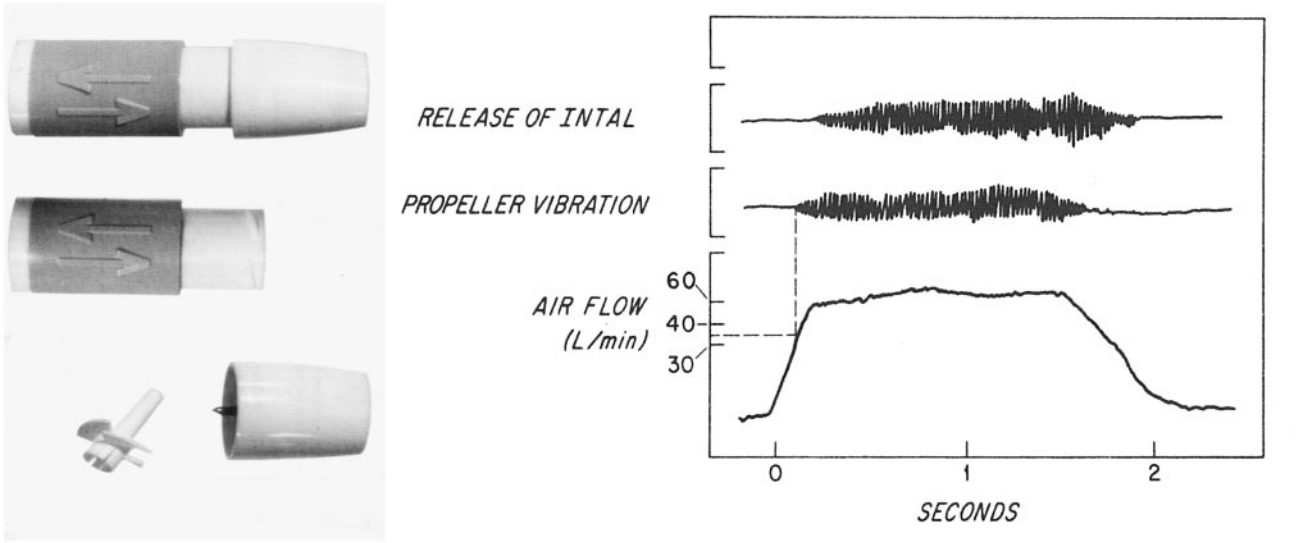

Fig. 5. The SpinHaler, a dry powder inhaler to deliver cromolyn sodium, reported in 1971 by Bell et al.[10] (Based on data from Reference 11.)

led to the development of spacer devices (add-on tubes with no valves) and holding chambers (extension tubes with 1-way inspiratory valves to contain the aerosol). This distinction in terminology between "spacer" and "holding chamber" is based on a presentation of Dr Myrna Dolovich at the Drug Information Association meeting on spacer devices in 1995.[12]

In 1976, an early breath-actuated MDI system was developed to simplify the coordination of actuation and inhalation, but the device required almost 50 L/min of inspiratory airflow to operate.[13] In 1978, Folke Morén investigated the effect of spacer tube design on delivery of pressurized MDI aerosols.[14] Newman et al had also noted that a high proportion of the fast-moving and larger MDI aerosol particles deposit in the orophyarynx, not in the lungs.[15] In 1981, Newman et al examined the deposition of MDI aerosol, using small (10-cm long) and large (750-mL) "extension" devices.[16] Their results showed unchanged alveolar deposition, but initial oropharyngeal deposition was reduced from 82% with the MDI alone to 57% with the large-volume pear-shaped spacer.

In 1982, at the conference of the American Association for Respiratory Care, held in New Orleans, Louisiana, Dr Martin Tobin graphically described the lack of patient coordination in using MDIs, and introduced the InspirEase drug delivery system for MDIs (Fig. 6).[17] The advantages of this spacer device were its relatively small size, collapsibility, the presence of an airflow signal to warn of too high an inspiratory flow, the separation of MDI-actuation from inspiration, and reduced oropharyngeal drug loss. The disadvantages were cost of an additional device to use an MDI, and the need to assemble the device. In fact, the original version required 2 different mouthpieces with MDI nozzle receptacles, to match different MDI drug canisters.

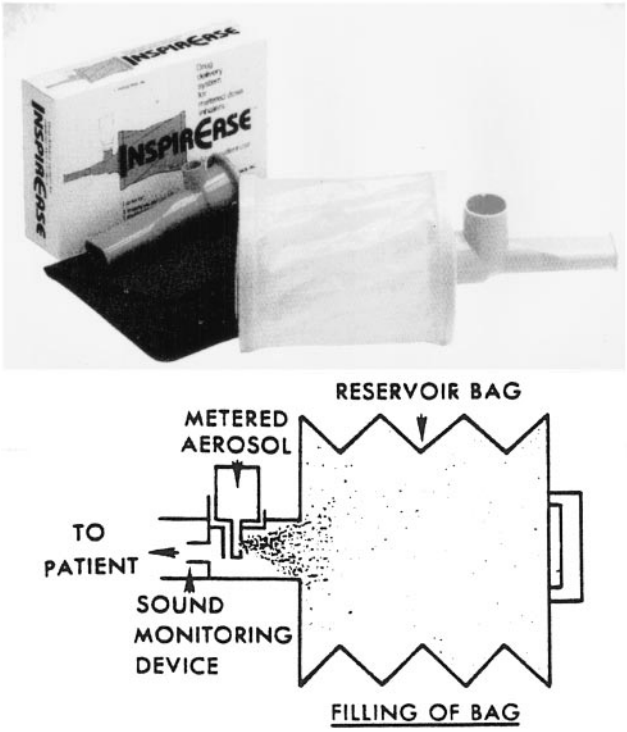

Fig. 6. The InspirEase, an early spacer system to facilitate use of metered-dose inhalers and reduce oropharyngeal aerosol deposition.

Subsequently in 1983, Dolovich et al reported the clinical evaluation of a simple "demand inhalation MDI aerosol delivery system," which was the early version of the AeroChamber from Monaghan Medical Corporation.[18] This was a true holding chamber; that is, the chamber contained a 1-way inspiratory valve, so that aerosol was released

Table 1. Recommended Aerosol Studies, Listed in Order of Priority, From the 1974 Sugarloaf Conference on the Scientific Basis of Respiratory Therapy

1. Determine regional deposition of nonhygroscopic stable aerosols, in both normal subjects and in patients with COPD
2. Determine the effect of water vapor in patients with COPD
3. Determine the physicochemical properties of bronchial secretions
4. Conduct studies on bronchodilators
5. Conduct studies on corticosteroids

COPD = chronic obstructive pulmonary disease

only when the patient inhaled from the chamber. Throat deposition (as measured with an aerosol radiolabeled with technetium) was reduced from 65% with the MDI alone to 6.5% with the AeroChamber, in bronchitic subjects. The AeroChamber, a 145-mL cylinder, incorporated a rubberized opening into which fit the MDI's mouthpiece actuator (or "boot") regardless of MDI actuator shape. There was no need for different nozzle receptacles to accommodate different MDI drug nozzles. A vibrating reed warned users of excessive inspiratory airflow.

The Need for Scientific Evidence With Inhaled Drug Delivery

In the early 1970s there was little scientific or clinical evidence on the increasingly widespread and popular use of inhaled aerosols, especially with nebulization of a variety of agents. On May 2–4, 1974, a landmark conference was held in Philadelphia, Pennsylvania, examining the scientific basis of respiratory therapy. The conference came to be called the "Sugarloaf Conference," because of the site where it was held, and its proceedings were published in the December 1974 supplement of *American Review of Respiratory Disease*. The final report on aerosol therapy noted that there was a need for mathematical models of pulmonary distribution of aerosols, "with actual studies of deposition using various breathing patterns."[19] The report called for studies with both normal subjects and patients with chronic obstructive pulmonary disease. There was a call to determine "output characteristics of aerosol-producing devices," including mass median diameter and dose delivered. Table 1 lists the recommended studies, in order of priority.

The 1974 Sugarloaf Conference was followed 5 years later by the 1979 Conference on the Scientific Basis of In-Hospital Respiratory Therapy. The final report on aerosol and humidity therapy again noted problems, including: difficulty in estimating or measuring the dose of a drug given via aerosol; lack of adequate information on particle-size distributions produced by aerosol generators and nebulizers; failure of different nebulizers to provide a reproducible dose; patients' difficulty with MDIs in releasing the proper dose at the correct time; and the possibility that aerosol generators and nebulizers can be contaminated and act as sources of nosocomial infection.[20]

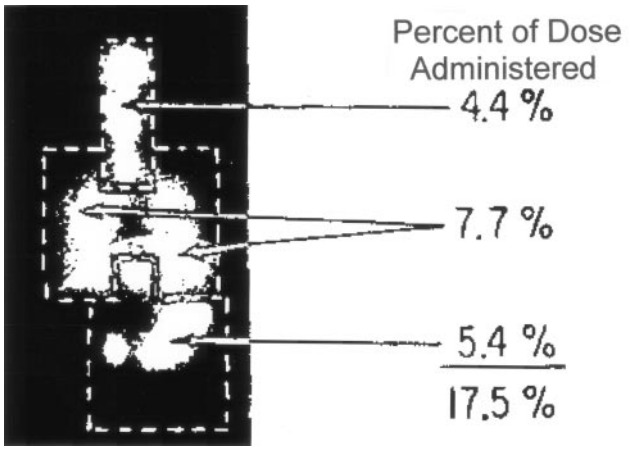

Fig. 7. Anterior scintigram showing distribution of radiolabeled aerosol in the respiratory tract and stomach. The aerosol was delivered by an intermittent positive-pressure breathing device with a jet nebulizer. The lung deposition was 7.7%. (From Reference 21, with permission.)

Early Data on Modern Aerosol Devices

Even before the 1974 Sugarloaf Conference, there were studies that began to provide scientific data and raise critical questions about aerosol therapies. In 1973, Irwin Ziment published an article in RESPIRATORY CARE, entitled "Why Are They Saying Bad Things About IPPB?" [intermittent positive-pressure breathing] He offered his own unpublished data that with IPPB only 7.7% of radiolabeled saline was deposited in the lungs of a normal volunteer (Fig. 7).[21] Although Ziment was concerned more with IPPB therapy than nebulizer therapy in that article, his data supported the trend calling for quantitative scientific measurement of aerosol therapy, which was seen in the Sugarloaf Conference the following year.

Further scientific evidence on aerosol therapy began to accumulate in the literature after the 1980 publication of the proceedings of the second conference on respiratory therapy. Stephen Newman et al published their classic and oft-referenced study on the disposition of aerosol drug from a pressurized MDI.[15] Their measurement of 8.8% lung-deposition of the total MDI dose was similar to Ziment's data from 1973 for IPPB/nebulizer delivery. In the study by Newman et al, 80% of MDI drug was lost to the oropharynx, and 9.8% was retained in the MDI mouthpiece-actuator (Fig. 8). These early studies began to alert clinicians to the relative inefficiency of aerosol delivery devices.

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