Aerosol Therapy of Reversible Airflow Obstruction
Concepts and Clinical Applications
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Aerosol therapy is the most beneficial approach to treating reversible airflow obstruction (RAFO) because it provides effective therapy with minimal side effects. As a result of developments in pharmacotherapy and aerosol delivery systems, it is now possible to provide maintenance therapy for RAFO in the majority of patients, virtually without the need to use oral agents. Commonly used or soon to be available aerosols are listed in Table 1. Even during exacerbations of asthma, adrenoceptor agonist aerosols are increasingly accepted as the treatment mode of choice rather than intravenous administration of the same drug. Also, the common and sometimes serious side effects of the systemic route are avoided by using aerosols.

Why Aerosols?

Aerosols provide increased drug bioavailability to the airway, and thus a greatly increased therapeutic/toxic ratio. As such, they have been demonstrated to be more effective than adrenoceptor agonists given orally for preventing exercise-induced asthma, for reducing airway hyperreactivity and for providing greater bronchodilatation than intravenous therapy. Aerosolized metaproterenol is significantly more effective than the oral form of the same drug or theophylline for achieving bronchodilatation in asthmatic patients, while combining the oral medication with the aerosol provides little if any significant benefit compared with the aerosol alone. These data are of particular clinical significance since oral therapy with adrenoceptor agonists or theophylline derivatives is associated with often unpleasant and sometimes serious side effects in many patients. Similarly, inhaled steroids such as beclomethasone have been very effective in asthma prophylaxis, allowing systemic steroids to be reserved for life threatening exacerbations and for the minority of patients with very severe asthma in whom the steroid-sparing effect of the aerosols is incomplete.

This form of therapy has been placed on a sound footing in recent years because of an increasingly close association between chest physicians, pharmacologists, and aerosol physicists whose research has produced improved pharmacologic agents and aerosol delivery systems.

Aerosol Behavior

Physical Determinants

Therapeutic aerosols generated by jet nebulizers or the pressurized metered-dose inhaler (MDI) produce particles in a size range between 0.5-35 micrometers (μm). However, only a small fraction of the generated aerosol, that between 1-5 μm, is efficiently deposited in the lower respiratory tract. This represents about 10-12 percent of the output from an MDI and 1-5 percent of that from most jet or ultrasonic nebulizers which is actually deposited below the larynx in the pulmonary airways. Nevertheless, in spite of the inefficiency of these aerosol systems, minute but highly effective doses of drug are deposited onto the respiratory tract mucosa.

Why is aerosol delivery to the lung so inefficient? The answer to this lies in an appreciation of aerosol physics and in the inherent efficiency of the airway as an aerodynamic particle filter.

Aerosols are characterized according to their mass median aerodynamic diameter (MMAD)* and the geometric standard deviation, the latter being an indication of the distribution of particle diameters within the aerosol. The aerodynamic diameter

*MMAD is the diameter of a unit density sphere having the same terminal settling velocity in air as the particle of interest regardless of shape or density.

Table 1—Aerosol Therapeutics

<table>
<thead>
<tr>
<th>Class of Drug</th>
<th>Generic</th>
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<tbody>
<tr>
<td>Bronchodilators</td>
<td>fenoterol, salbutamol,</td>
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<tr>
<td>Adrenoceptor agonists</td>
<td>terbutaline, bitolterol</td>
</tr>
<tr>
<td>(relatively β2 specific)</td>
<td>ipratropium bromide, atropine</td>
</tr>
<tr>
<td>Anticholinerges</td>
<td>methyl nitrate</td>
</tr>
<tr>
<td>Anti-inflammatory/anti-allergic</td>
<td>sodium cromoglicate,</td>
</tr>
<tr>
<td></td>
<td>beclomethasone dipropionate,</td>
</tr>
<tr>
<td></td>
<td>budesonide, flunisolide,</td>
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<tr>
<td></td>
<td>triamcinolone acetate</td>
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*Aerosol Therapy of Reversible Airflow Obstruction (Newhouse, Dolovich)
indicates where in the airway particles are most likely to be deposited and the mechanism by which the deposition occurs.

Aerosols are deposited in the airway as a result of three main physical mechanisms:
1. Impaction. This results when inertial forces, acting chiefly on particles greater than 5 μm, cause them to deposit on the walls of the upper airway, larynx and the first few bronchial divisions. This effect is more marked at high inspiratory flow rates and in airways with reduced diameter, such as in patients with airflow obstruction.
2. Sedimentation. Smaller particles, in the size range 3-1 μm, are deposited mainly by sedimentation due to gravitational forces.
   This occurs chiefly in regions of low airflow between the 10th and 17th bronchial division and is the most important mechanism governing the deposition of therapeutic aerosols.
3. Diffusion. Smaller particles, mainly those below 0.1 μm, are deposited with increasing efficiency as a result of Brownian forces (diffusion). However, their mass is very low and their therapeutic potential, while not yet well explored, is probably not great.
   Particles between 1-0.5 μm may penetrate into respiratory bronchioles or even alveoli. However, few of these deposit in the lungs, as they are influenced little by gravitational or Brownian forces. They are, therefore, not well suited for therapeutic purposes.
   Thus, for treating RAFO, aerosols in the 1-5 μm size range are optimum and these are produced by many commercially available jet and ultrasonic nebulizers or metered-dose inhalers. Aerosols intended for nasal deposition often have a coarser particle size for improved deposition by impaction, while those aerosols designed to penetrate deeper into the lower respiratory tract are finer in size in order to minimize large airway deposition.

AEROSOL INHALATION

Physiopathologic Factors

The respiratory variables, ie, inspiratory flow rate, frequency of breathing and tidal volume, and pathologic abnormalities, particularly airway narrowing, act upon the respirable aerosol to affect aerosol retention and penetration into the airway and hence clinical response. Since it is the inspiratory flow rate that provides the energy which carries an aerosol into the lung, the greater the flow rate, the greater the particle inertia. Thus, at high flow rates (over 1 L/sec), therapeutic aerosols tend to be increasingly deposited in the upper airway instead of being carried deeply into the lung. Similarly, since the respiratory frequency determines the residence time of particles in the airway and this in turn governs the time available for particle sedimentation onto airway walls, the lower the respiratory rate (the longer the breath-holding time), the greater the airway particle deposition. The beneficial effect of a greater tidal volume on aerosol penetration into the peripheral airway seems obvious. However, as turbulence in the upper airway, larynx and large intrathoracic airways causes efficient particle mixing with the air in the lung during inspiration, tidal volumes more than two-three times the dead-space have relatively little additional effect on aerosol distribution. Airway narrowing due to bronchospasm, edema and retained secretion as well as structural changes in the airway may be of major importance preventing particle penetration into more peripheral airways. It is probably largely for this reason, as well as the associated increased inspiratory flow rates and tachypnea that much larger doses of bronchodilator medication must be used during severe asthmatic episodes.

AEROSOL DELIVERY SYSTEMS

MDI, Nebulizers, IPPB, MDI Add-on Devices

For aerosol therapy, four types of delivery systems are in current clinical use:
1. Metered dose inhalers
   a) fluorocarbon (Freon) propelled
   b) dry powder
2. Ultrasonic or jet nebulizers
3. MDI with add-on extension device or valved aerosol holding chamber
4. Intermittent positive pressure device and nebulizer

None of the more costly and complicated methods for providing aerosol therapy have been shown to have any inherent advantages over the technically sophisticated but cheap and convenient MDI. Of sole importance is the dose of medication delivered to the airway regardless of the delivery system, provided the latter can achieve reliable delivery of a predictable dose. Thus, aerosol therapy with compressor or compressed gas cylinder driven nebulizer is being replaced by the MDI except in patients unable or unwilling to use MDIs. Accumulating evidence during the past ten years, culminating in a recent multi-center trial in more than 1,000 patients studied for three years, has demonstrated conclusively that there is no advantage to IPPB delivery of aerosols. The only exception may be the treatment of croup with epinephrine or laryngeal candidiasis with nystatin where the high inspiratory flow rates provided by IPPB may be used to increase delivery of these drugs to the larynx. It should be emphasized that there is no rationale whatever for the practice still common in some centers, of providing IPPB or nebulizer-delivered bronchodilator aerosols to out-patients three or four times a week. The advantages of MDI are listed in Table 2.
While IPPB aerosol therapy has largely been abandoned, therapeutic aerosols are still commonly produced by jet and ultrasonic nebulizers in hospital practice, mostly in the emergency room and on the wards. Since there is no evidence that aerosol delivered in this way provides better or more prolonged bronchodilatation than aerosols inhaled from MDIs and since nebulizer treatments are inevitably more costly and take longer to provide for the acute asthmatic than MDI puffs, there is never any reason to use nebulizers unless the MDI cannot be administered to the patient. The notion that bronchodilator aerosols delivered by nebulizer in life-threatening asthma are superior to aerosols generated by MDI probably relates in part to the five-to-ten fold greater dose recommended for nebulizer administration compared with the usual two puffs of MDI recommended for maintenance therapy but commonly used in acute severe asthma as well. Sixteen puffs (equivalent to 4 mg) of terbutaline administered by MDI to patients with life-threatening asthma was shown to be as effective as the same dose of nebulized drug. Since it has been demonstrated in studies using radiolabelled drug solutions that MDIs are, on average, two-to-three times more efficient than nebulizers, even smaller MDI doses might suffice. Thus, aerosols can be provided using an MDI even to patients with severe acute asthma, for a considerable saving in time and cost, but the usual dose must be augmented three-to-six fold.

There will, nevertheless, be a number of patients who, because of their marked dyspnea, anxiety or poor hand/breath coordination, unable to inhale aerosol from a MDI administered in the usual way. Infants, children, the handicapped and elderly may also have problems using the MDI unaided. In such patients, aerosol therapy can usually be accomplished by means of MDI add-on devices such as the Aerochamber, a relatively foolproof 130 ml valved aerosol holding chamber into which the aerosol can be sprayed and from which the patient can inhale the medication without the need to precisely coordinate aerosol discharge and inhalation. The Aerochamber is an 11 x 4 cm particle size selective aerosol holding chamber that augments the number of available particles in the respirable range below 2.5 μm while reducing delivery to the upper airway of larger, nonrespirable particles from 80 percent to about 10 percent of the output from an MDI. These devices can be used not only in the emergency room, but also throughout the hospital on a regular basis for aerosol administration by nurses or physiotherapists, since their simplicity obviates the need for the special skills usually provided by the respiratory technologist. Compared with nebulizers or IPPB-delivered aerosols, the combination of MDI plus holding chamber results in considerable cost benefit while at the same time assuring reliable and more efficient aerosol therapy. Aerosol holding chambers also decrease cough during aerosol inhalation in those patients with very marked airway hyperreactivity and virtually eliminate dysphonia and laryngeal candidiasis in patients on steroid aerosols. Recent studies have also shown that significantly more patients with asthma could be taken off systemic steroids when beclomethasone was administered via an Aerochamber compared with unaided MDI administration of the steroid aerosol. The advantages of MDI with a valved add-on device for steroid aerosol therapy are summarized in Table 3.

Since the introduction of the Aerochamber to clinical practice about five years ago, several similar devices, most of them considerably larger, have been introduced. However, increasing the holding chamber size simply makes the device more inconvenient without significantly augmenting performance. Recently, the addition of a well-fitting mask to the Aerochamber has allowed successful MDI aerosol therapy in infants and children under three years of age, making it unnecessary to use nebulizers or oral bronchodilator therapy even in this group of patients.

Clearly, MDIs are the cheapest, simplest and most effective way of delivering therapeutic aerosols. However, there has been a great deal of controversy about the best way of using these devices for most effective therapy, particularly with respect to whether aerosol inhalation should take place with the actuator mouthpiece held within the closed lips or 3-4 cm in front of the open mouth.

Using radioactively-labelled MDI generated aerosols, Dolovich et al demonstrated that MDI aerosols are best administered as outlined in Table 4.

Since this technique provides about twice as much medication to the lower respiratory tract than the closed-mouth method still advocated by many physicians and most drug company package inserts, we think it unfortunate that many patients are still being

Table 2—Advantages of MDI

<table>
<thead>
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<th>Advantage</th>
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<tr>
<td>Portable, rapidly available</td>
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<td>Simple to use (in most patients if adequately instructed)</td>
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<tr>
<td>Inexpensive</td>
</tr>
<tr>
<td>Efficient nebulization of medication</td>
</tr>
<tr>
<td>Protects contents from physical, chemical, biologic contamination</td>
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Table 3—Advantages of MDI with Valved Add-on Device (Aerochamber) for Steroid Aerosol Therapy

<table>
<thead>
<tr>
<th></th>
<th>Candida Infection</th>
<th>Candida Colonization</th>
<th>Oral Steroids Withdrawn</th>
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<tbody>
<tr>
<td>MDI</td>
<td>4 pts (22%)</td>
<td>12 pts (67%)</td>
<td>6 pts (33%)</td>
</tr>
<tr>
<td>MDI and Aerochamber</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0 pts (0%)</td>
<td>3 pts (17%)</td>
<td>12 pts (67%)</td>
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*Adapted from ref 31
taught to use their MDI by closing their lips around the mouthpiece, breathing from residual volume and inhaling at relatively high inspiratory flow rates. The benefit of the open mouth technique is probably due to the approximately 130 ml aerosol holding chamber provided by the oral cavity and the 10-12 cm from the actuator to the pharynx, allowing deceleration of larger aerosol droplets and evaporation of Freon. Thus, a greater proportion of the aerosol cloud becomes respirable resulting in a greater response to the drug. 30

AEROSOL THERAPY IN ASTHMA

A Clinical Perspective

The objectives of effective asthma therapy are outlined in Table 5.

In many of our patients on maintenance therapy, two-four puffs of adrenoceptor agonist are prescribed up to six times a day if needed. During acute life-threatening episodes, four puffs of the sympathomimetic are administered over about two minutes followed by one puff a minute until the breathlessness improves or unpleasant tremor limits further administration. This approach obviates the need for nebulizer delivered bronchodilator solutions in most patients. Ipratropium bromide may also be given during such acute episodes. 31 To determine the dose, we have used the number of puffs of sympathomimetic bronchodilator required to achieve benefit and/or tremor as a guide to administering a matching number of puffs of ipratropium. Frequently, untrained, confused or anxious patients will abuse their MDI, exhausting a 200 puff canister in very few days. This may indicate very poor technique (delivering the aerosol at total lung capacity or breathing in too quickly), unnecessary administra-

Table 5—Objectives of Asthma Control

Virtual freedom from ongoing symptoms
No symptoms on exposure to cold air, exercise or at night
No life threatening episodes
Patient self-care of exacerbations with short courses of systemic steroids
Detailed written instructions to improve understanding and compliance
Virtual absence of side effects by using aerosols and drug combinations

tion of multiple puffs at a time, or deterioration of the asthma. We try to train patients to recognize such “abuse” as a warning signal of deterioration and to initiate a course of systemic steroids if the adrenoceptor aerosol is needed more than six times in 24 hours for more than two consecutive days or if the bronchodilator effect lasts consistently less than four hours. In patients suspected of using their MDI poorly, addition of a valved MDI add-on device frequently reduces the rate of MDI consumption. In our tertiary referral center, the daily administration of as little as 400 µg of beclomethasone is unusual, since our patients, who for the most part have more severe asthma, frequently require 800 µg or even 1,200 µg daily for adequate control. Thus, most of our asthmatic patients can be managed for long periods of time with aerosol therapy alone, and with the addition of short bursts of high dose rapidly decreasing systemic steroids for exacerbations. During such episodes, patients are advised to continue therapy with beclomethasone aerosol in addition to systemic steroid therapy to obviate the confusion that often results from frequent changes in medication and to assure a smooth transition to aerosol therapy alone, once the acute episode has resolved. Similarly, if patients’ asthma is symptomatic when prophylactic aerosol therapy is initiated, one-two weeks of systemic steroid therapy (prednisone 30 mg/d) is usually given before aerosol therapy with cromoglicate or steroids is started.

THERAPEUTIC STRATEGIES

Recent studies have shown that spreading the total bronchodilator aerosol dose over 30 minutes provides significantly more bronchodilation than giving the entire dose at once. 41 This is quite inconvenient and is probably only of relevance in very difficult to manage asthmatic patients whose control is marginal, even though all therapeutic modalities are being maximally applied. We do recommend, however, that patients allow about five minutes to elapse between administration of the bronchodilator and steroid aerosol to assist deeper penetration of the latter into the lung. This should be advantageous on theoretic grounds even though there is, as yet, little objective evidence of significant additional benefit. 41

In general, the more complex the instructions given to patients, the less likely are they to remember them. We therefore try to simplify therapy as much as possible to improve compliance. Thus, most patients on aerosolized steroids achieve as effective control on bid as qid dosing. 41 making the former preferable for long-term management.

It has recently been appreciated that cough associated with respiratory infections is usually related to airway hyperreactivity. 42 Thus, bronchodilator aerosols may be superior to cough suppressants for therapy.
Furthermore, chronic cough or recurring episodes of cough may be an asthma equivalent, best treated with aerosolized bronchodilators, steroids or sodium cromoglycate. An adrenoceptor agonist inhaled 5-10 minutes before exercising will usually prevent exercise induced asthma for several hours. If protection is nevertheless incomplete, the addition of two-four puffs of sodium cromoglycate will almost always suffice. Ipratropium bromide, a new anticholinergic aerosol, is now finding a place in the therapy of reversible airflow obstruction. It has been found useful in some patients with chronic bronchitis, emphysema and sometimes in asthmatic patients, particularly the occasional patient in whom adrenoceptor agonist side effects are very bothersome. In acute asthma, the combination of ipratropium with an adrenoceptor agonist was shown to be significantly more effective than the adrenoceptor agonist alone. Ipratropium may also be useful for the management of rhinorrhea in vasomotor rhinitis and during the first three days of the common cold when watery rhinorrhea is particularly bothersome.

ASSURING PATIENT COMPLIANCE

Achieving compliance with the prescribed regimen in ambulatory patients is one of the greatest challenges of medical therapy and this is particularly true of aerosol treatment. This is the case not only because many patients initially find aerosol devices unfamiliar and difficult to use, but also because, in contrast to bronchodilator therapy, from which patients achieve rapid response, prophylactic therapy with cromoglycate or steroid aerosols is an act of faith which must usually be continued, for long periods of time, despite relative freedom from symptoms. Consistent and frequently repeated instruction and a “show me” approach to MDI use at follow up visits is essential if effective asthma control is to be achieved.

If patients nevertheless have problems manipulating the MDI, asthma control may remain suboptimal, despite apparently adequate doses of therapeutic agents. To correct this difficulty and aerosol steroid side effects, especially if hoarseness or thrush are a problem, valved MDI add-on aerosol delivery systems should be used. These devices make all classes of aerosol therapy reliably available to virtually everyone at low cost, making nebulizers and therapy by the oral, rectal or intravenous route almost unnecessary, except the latter during severe life threatening episodes.

FEAR OF AEROSOLS?

Physicians’ fear of recommending more than two puffs of adrenoceptor agonist aerosol from an MDI (while being quite comfortable with five to ten times the dose by jet nebulizer or orally) is probably a holdover from the fear that, during the 1960s, self-administration of isoproterenol from MDI accounted for excess asthma deaths in Britain and Australia. During the past 15 years, however, despite a four-fold increase in MDI sales, mortality due to acute severe asthma has again decreased to pre-1960 levels. While it is not certain what caused the excess deaths, it is now believed that much of the problem may have been due to excessive reliance on the transient relief provided by frequently administered isoproterenol so that patients failed to seek more definitive therapy with high dose systemic steroids before their condition had deteriorated severely.

AEROSOLS—THE FUTURE?

It is unlikely that we will see further major advances in selective beta, adrenoceptor agonists except perhaps to extend their duration of action. This would, however, be particularly useful since one of the major problems of asthma management remains the control of nocturnal symptoms—perhaps the major remaining indication for sustained release theophylline in some patients. So far, attempts to find superior analogs of sodium cromoglycate have been notably unsuccessful. Recently, studies of calcium channel blockers have shown these to be somewhat effective in exercise or cold air-induced bronchospasm although adrenoceptor agonists are superior. We await more bronchial smooth muscle specific agents which may have a more potent effect.

Nearly 20 years of prostaglandin research has so far failed to yield anything clinically useful for asthma therapy. However, the lipoxygenase pathway of arachidonic acid metabolism has, in the past five years, been the subject of intense interest. While it is too early to be sure, it seems likely that leukotriene antagonists may eventually find a place in clinical practice. It is probable that new research avenues, aimed at a better understanding of smooth muscle contractility will lead to new and potent pharmacologic agents for treating reversible airflow obstruction.

Already available in Europe and hopefully, soon in North America, are the high dose beclomethasone or budesonide aerosols (250 μg and 200 μg per puff respectively). These will likely replace multiple puffs of the standard 50 μg dose, particularly in those patients presently on 16-32 puffs of beclomethasone daily. This should allow the practical application of even larger doses by aerosol which have, in European studies, permitted a further reduction or even elimination of systemic steroid therapy in some of the remaining systemic steroid dependent asthmatics, fortunately without incurring notable additional side effects.

CONCLUSION

Aerosols are used increasingly for the management of RAFO because they have a high biologic activity...
locally in the airway and thus an excellent therapeutic/toxic ratio. As physicians appreciate the need to individualize the dose to the requirements of the individual patient and the varying severity of the disease, and assure aerosol delivery to the site of action in the lower respiratory tract, aerosols will probably become the overwhelming therapeutic choice for the management of RAFO in adults and children.

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