Aerosol Therapy

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ABSTRACT

Aerosol therapy has revolutionised the treatment of several respiratory diseases including obstructive airway diseases. This form of therapy refers to delivery of the drug directly into the lower airways for either topical or systemic effect. The greatest advantage of this form of therapy is the use of smaller doses and thus, minimal systemic adverse effects, besides giving a rapid response. Aerosol therapy is now also being used for systemic delivery of certain medications, such as insulin. The particle size (expressed as mass median aerodynamic diameter) is of critical importance as the drug delivery depends on the same to a major extent. Several devices such as metered dose inhaler (MDI), dry powder inhaler (DPI) and nebulisers are available. Each of these devices have advantages and disadvantages that needs to be understood for optimising the benefit. Aerosol therapy is also used in patients on mechanical ventilation for bronchodilator therapy, anti-inflammatory medication and at times for instillation of antibiotics and mucolytics. A knowledge of principles and applications of aerosol therapy is essential for its effective use in various conditions. [Indian J Chest Dis Allied Sci 2008; 50: 209-219]

Key words: Lung, Obstructive airway disease, Asthma, Bronchodilators, Aerosol therapy.

INTRODUCTION

Aerosol therapy refers to the delivery of a drug to the body via the airways by delivering it in an aerosolised form. Whereas the aerosolised drug may be intended for systemic use utilising the vast surface area for absorption provided by the respiratory tract, the overwhelming majority of the aerosols are meant for topical use. Evidence of use of aerosol therapy has been found during the days of Hippocrates1 who utilised hot vapours for the management of respiratory diseases. However, the modern era of aerosol therapy began with the introduction of the Medihaler Epi in 1956.2 The last few years have seen a major evolution in our understanding of aerosol delivery to the human subjects. Modern technology along with increasing understanding of human pulmonary physiology has aided the development of improved systems of aerosol delivery. This form of therapy has revolutionised the management of patients with various pulmonary diseases. More and more bronchodilators and anti-inflammatory agents are becoming available for use as aerosol therapy. We attempt to summarise the basic principles of aerosol therapy and the equipments used for generation of aerosols, their clinical uses and limitations.

PRINCIPLES OF AEROSOL THERAPY

The basic advantage of aerosol therapy lies in the delivery of high local concentrations of the drug directly to the site of action with minimised risks of systemic effects. This is achieved with a much lower dose compared to what may be required for systemic administration for equivalent therapeutic response. The commonest aerosolised drugs are the bronchodilators and anti-inflammatory agents used for obstructive airway diseases, such as asthma and chronic obstructive pulmonary disease (COPD). Their efficiency results from local effects in the airways.3 High local concentration of these agents in the lung maximises their intended effects and minimises systemic absorption and the potential adverse reactions. Another advantage of this mode of drug delivery is the rapidity of onset of action after the drug is inhaled as compared to other modes of delivery. Certain other drugs, such as antibiotics, may also be used for local effect in the lung parenchyma in patients with infectious diseases, such as pneumocystis carinii pneumonia.

An understanding of factors affecting delivery of aerosols is essential before using them. The pulmonary deposition of aerosol is achieved by way of three key mechanisms, namely inertial impaction, sedimentation and diffusion. These three mechanisms operate in different combinations for different aerosol drugs at different sites in the pulmonary tree. Whereas inertial impaction is the predominant process in the oropharynx and the larger airways for aerosols with relatively large particle size (>3μ), diffusion by way of Brownian motion is the dominant mechanism for the smaller sized

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aerosols (<0.5µ). Aerosols with the particle size in the range of 1-3µ are subject to gravitational sedimentation in the small airways and the same tends to be enhanced by breath holding. The fraction of drug eventually delivered at the desired site of action also depends on the physical properties of the aerosol and also the host factors that include pattern of ventilation, status of the airways and lung mechanics (Table 1).

Table 1. Factors affecting delivery of aerosolised drugs to the lungs

<table>
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<th>Physical Characteristics of the Aerosol Particle</th>
<th>Host Factors</th>
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**Physical Characteristics of Aerosol**

Physical characteristics of aerosol particles including the size (diameter), density, electrical charge, hygroscopy, shape and the velocity of the aerosol have an impact on the deposition of the aerosol. These characteristics are dependent on several factors, namely the drug being used, its formulation and the device or the aerosol generator. For example, a solution based formulation of an aerosol generates much smaller sized particles (~2µ) as compared to suspension based formulations where particles size is in the range of 4µ are generated. These characteristics become pertinent since among the various physical characteristics, droplet size of the aerosol is the most important factor in the delivery of the drug to the lungs. Size of the aerosol droplets is generally characterised by mass median aerodynamic diameter (MMAD). The MMAD of an aerosol refers to the particle diameter that has 50% of the aerosol mass residing above and 50% of its mass below it. Any droplet with MMAD larger than 5µ is likely to be filtered out in the upper airways and fail to reach even the larger airways. Aerosol particles less than 5µ in size readily reach the distal areas of the respiratory tract. This relationship holds true up to a droplet size of 0.6µ beyond which the smaller particles tend to be exhaled out. A particle size less than 2µ is ideal and is able to percolate right up to the peripheral airways. Therefore, it is no surprise that most of the commercially available nebulisers produce droplets of roughly this size. Chemical and physical properties of the drug may also play an important role in determining the penetration of the aerosol. Aerosols containing drugs with hygroscopic properties are likely to increase in size in humid conditions that may adversely impact the delivery of the drug.

Another characteristic that may modify the penetration of the drug is the shape of aerosol where a more aerodynamically shaped droplet is likely to be associated with greater penetration. Finally, the velocity at which the aerosol is generated also affects the fraction delivered to the lower airways. Those aerosols that are generated at a very high velocity tend to get deposited in the upper airways and consequently the delivery to the lower airways is compromised. An MDI is a typical example of a generator that produces aerosols at a high velocity, which are in the range of 10-100 m/s. On the other hand, dry powder and nebulizers produce aerosols with relatively low velocities. Slower flow minimises oropharyngeal and upper airway deposition and enhances distal delivery and deposition.

**Host Factors**

Host factors comprise of those related to the ventilatory and the airway status of the patient. Among ventilatory factors that have been shown to be important are: (i) inspired volume, (ii) inspiratory time, (iii) breath-hold duration, and (iv) timing of aerosol delivery during inspiration. Inspired volume plays a critical role in the delivery of the aerosolised drug. With increasing volume of inhalation, particles are more likely to be carried further into the lungs. Hence, instructions are given to patients to take a deep breath with the actuation of aerosol delivery device. They are also instructed to exhale to functional residual capacity (FRC) before initiating inspiration. However, forced exhalation to residual volume prior to inhalation is not recommended since this may lead to temporary collapse of some airways and reduce delivery of the drug. It has been shown that breath holding is important in maximising the drug delivery. Breath holding increases the penetration as well as the number of particles deposited in the lungs. However, the duration for which the breath should be held has been debated. A study by Newman and colleagues showed that a four-second hold is extremely helpful in improving the delivery of the drug whereas a longer duration may not help. The mechanism of increased penetration of aerosol particles is not fully understood. To elucidate the role of breath hold, Darquenne and colleagues compared the penetration of aerosol bolus inhalations of 1-µm-diameter particles with a period of breath hold on the ground with penetration of similar aerosol particles under conditions of microgravity (to eliminate the effect of gravity). It was demonstrated that deposition was independent of breath-hold time in microgravity, whereas on the ground, deposition increased with increasing breath-hold time. This provided an indirect evidence of role of gravitational sedimentation as the main mechanism of deposition and dispersion of
aerosol during breath holds. Finally, while using an MDI, it is important to coordinate inspiration with the actuation of the inhaler. An uncoordinated actuation may lead to loss of most of the drug. This is not a major factor while using aerosol generated by other equipments, such as nebulisers.

Among the airway factors, status of the airways and the lung pathology do not affect the total amount of drug delivered to the airways but may play a major role in deciding the fraction of dose reaching the desired site. For example, increased airway resistance seen in patients with obstructive airway disease leads to the aerosol particles being deposited in predominantly proximal locations. In fact, even asymptomatic smokers also show a similar tendency of localising aerosol particles centrally, which may be due to goblet cell hypertrophy and increased mucous production seen in these subjects. This may be responsible for poor response to inhaled drugs in smokers as compared to non-smokers with similar severity of the disease. Chalmers and co-workers reported that in mild asthmatics response to inhaled steroids (fluticasone) was much better in non-smokers as compared to patients who continued to smoke while on therapy. This lack of response could be secondary to poor distal deposition of aerosol particles in smokers. However, importantly these problems have been shown to be overcome by using certain techniques that improve delivery of aerosol particles to the peripheral locations within the airways. The rate at which patient inspire, the timing of inhalation, and the period of breath-holding can be suitably modified to increase the fraction of aerosol entering the lungs at the desired locations. There is an inverse relationship between the patient inspiratory flow rates and the extent of peripheral deposition. Schiller-Scotland compared the deposition of aerosol particles in the size range between 1µ and 3µ in patients with obstructive lung disease and in normal people. It was shown that a breath holding interval of six seconds after inhalation reduced the difference in the deposition of aerosol particles between the two groups and thereby compensated for differences in airway resistance and lung mechanics. Therefore, the optimum inhalation technique for aerosol therapy is slow inspiration followed by breath holding for at least six seconds.

**AEROSOL DEVICES**

The devices available for generation of aerosols can be broadly divided into three categories: metered dose inhaler (MDI), dry powder inhaler (DPI), and nebuliser. Two types of nebulisers, namely, jet nebuliser and ultrasonic nebuliser are available for use as aerosol generators.

**Metered Dose Inhaler (MDI)**

The history of the MDI dates back to 1955. The first MDI included a 50µL metering device, a 10mL amber vial, and a plastic mouthpiece with molded nozzle to administer salts of isoproterenol and epinephrine. The next year, a surfactant and micronised powder were added to the propellant, creating the first commercially available formulation. Today the modern MDI (Figure 1) comprises of a pressurised metal canister containing a mixture of propellants, surfactants, preservatives, and the drug.

![Metered dose inhaler.](image)

Metered dose inhalers are the most commonly used devices for generation of aerosol. They consist of a micronised form of the drug in a propellant under pressure with surfactants to prevent clumping of drug crystals. Lubricants for the valve mechanism and other solvents are the other constituents. When the device is actuated, the propellant gets exposed to atmospheric pressure, which leads to aerosolisation of the drug. As it travels through the air, the aerosol warms up leading to evaporation of the propellant that reduces the particle size to the desirable range. The fraction of drug to the airways ranges from 5 percent to 15 percent.

Propellants used for aerosol generation in MDIs have generated some controversy. The conventional propellants used in these devices has been chlorofluorocarbon (CFC). In the year 1987, all substances that could deplete the ozone layer in earth’s atmosphere were banned. Chlorofluorocarbon is also known to cause this effect and hence came under the imposed ban. Although products used for medical purposes were exempted from the ban, newer propellants have been developed. Already MDI using newer propellant like...
hydrofluoroalkane (HFA) have become available. Substitution of HFA for CFC has resulted in critical changes in the pharmacokinetic profile of drugs, such as beclometasone used for aerosol therapy. Among other differences, the CFC based MDIs contain the drug in suspension form whereas the HFA ones have it in a solution form. Moreover, no surfactant is used in the HFA devices. However, alcohol is added for dispersal. The particle size produced by HFA based MDIs is finer and softer and is generated at slower speeds. Consequently, the oropharyngeal deposition is lesser with HFA based MDIs and delivery to lower airways is double compared to that of CFC based MDIs. It is no surprise that the major conclusion to come out of a study comparing the two different propellant based MDIs was that only 50% of the usual dose used in CFC MDIs was required to produce the equivalent clinical effect.

Metered dose inhalers have been popular because of ease of usage, small and compact size and the relative cost-effectiveness. On the other hand, the commonest error in the usage of an MDI is the lack of coordination between the actuation of the device and the initiation of inspiration. Many other problems can also be associated with the use of MDI. The physician who prescribes these devices should keep these things in mind and the same should be conveyed to the patient as well.

1. Even with the best technique, only 10% to 20% of the total drug makes it to the large airways and only 5% of the drug reaches the small airways.
2. Various additives and cold propellant in MDIs may cause airway irritation, that may lead to cough or occasionally, bronchospasm. Since the drug contained is usually a bronchodilator, this effect may not be revealed clinically and may manifest as a poor response to the treatment.
3. The medication is held in a suspension with the propellant in the canister. To prevent undesirable layering of the medication, it is imperative to shake the canister between each actuation.
4. It is important to keep in mind that the MDI may continue to deliver the aerosol even after the drug is finished. This aerosol consists only of the propellant at this time. This tends to occur usually in patients who do not shake the canister well as a routine. Since most manufacturers do not provide dose counters, patients must keep a track of the number of actuations. Such problems can be taken care of by noting the manufacturer’s recommended number of actuations and marking the estimated completion date.
5. Each actuation of the aerosol device leads to cooling of its contents temporarily. A 30- to 60-second pause between actuations is recommended so as to allow the device to re-warm as the predictability of the aerosol produced is poor when the contents are cool.

Steps for Ideal Use of an MDI

1. Shake the canister.
2. Hold the canister upright.
3. Gently exhale to functional residual capacity (do not exhale to residual volume).
4. Place the mouthpiece in mouth, between teeth, and close lips or keep the same 5 cm in front with mouth open.
5. With initiation of inhalation, actuate the canister
6. Slowly inhale up to the maximum capacity (total lung capacity).
7. Hold breath for 10 seconds or as long as possible.
8. Wait for at least 60 seconds before the next puff.

In breath-activated MDIs which have been available in the West, coordination between breathing and actuation is not required. These devices consist of a mechanical flow trigger that gets activated when inhalation flow reaches ≥ 30 L/min. However, a drawback is that the elderly patient may be unable to use this device.

Valved Holding Chambers/Spacers

To overcome the major problem related to coordination, a valved holding chamber may be used as an adjunct to the MDI (Figure 2). It is also useful for old patients and those who are unable to hold breath. This adjunct has many advantages including improved coordination with the inspiratory flow of the patient. When an MDI is used with spacer devices, reduction occurs in the overall particle size of the inhaled aerosol, as larger particles tend to stick to the chamber walls/valves. This also leads to a reduction in particle velocity leading to decreased upper airway deposition. It should be explained to the patient that the aerosol must be inhaled immediately after the MDI is discharged into the chamber and only a single actuation should be discharged into the chamber for each inhalation. Following this, the patient should be instructed to breath in and out for a few breaths before actuating another discharge of MDI. The reduced oropharyngeal deposition associated with the use of a spacer chamber is an advantage when using corticosteroid MDIs as the local adverse effects are then much less likely to occur. In spite of all these advantages, it has been shown...
that no extra benefit in terms of delivery is achieved by using a spacer device by the patients who follow the correct technique with MDI alone.\textsuperscript{24} Holding chambers are also not totally free of problems. Electrostatic charge develops on the inside of the chamber due to regular washing and drying and affects delivery of larger particles. Patients should be instructed to dry the chamber using a non-static cloth or to let it air dry. Another drawback of using the holding chamber is that the new HFA based MDI have not been evaluated with the presently available chambers. Because of the differences in the physical characteristics of the particles generated by HFA based MDI, drug delivered to the patient may be different.

**Dry Powder Inhalers (DPI)**

Dry powder inhalers (DPI) consist of pharmacologically active powder as an aggregate of fine micronised particles in an inhalation chamber (Figure 3). These aggregates are converted into an aerosol by inspiratory airflow through the inhaler generated by the patient. This basic fact excludes the problem of coordination between the delivery of the drug and the initiation of inspiration. But the very same fact also makes it unsuitable for patients who are unable to generate high inspiratory flow rates. Lack of requirement of propellant is an advantage of DPIs over MDIs. The fraction of the drug delivered to the site of action by a DPI varies from 9\% to 30\% and varies among different commercially available products.\textsuperscript{24,25} The DPIs tend to fail in patients who cannot generate moderate to high inspiratory flow rates since unlike the MDI, they are driven by the patient’s own effort. In a DPI, the aerosol needs to be generated from the powder formulation by patient’s own effort. For achieving this, a high turbulence is needed to break the large agglomerates of the drug into smaller, finer and inhalable particles. Turbulence is generated by creating resistance to air flow in the DPI device and the effort required to generate adequate flow rates is dependent on the extent of resistance. Whereas the flow rates required to be generated vary among various available DPIs, a flow rate of 60-90 L/min is generally required.\textsuperscript{26} This makes the use of DPI unsuitable for elderly as well as younger pediatric patients and those with severe bronchospasm. Some of the newer innovations in the field of DPI devices have attempted to circumvent this drawback. The device used for the recently launched inhaled insulin, Exubera\textsuperscript{9}, uses compressed air to aerosolise the insulin powder and converts it into a standing cloud in a holding chamber. Other environmental factors may also influence the extent of the drug delivered with DPI devices. High humidity and rapid changes in temperature may affect de-aggregation of the drug particles and reduce the fraction of the drug being delivered.\textsuperscript{27,28}

There is a wide range of DPI devices that are available for clinical use. The devices may be single dose device such as a Rotahaler\textsuperscript{®} where each dose needs to be loaded by the patient or the pre-loaded multi-dose device such as Diskus\textsuperscript{®} where the patient does not need to load the drug every time. More recently another multi-dose DPI device called Novolizer\textsuperscript{®} was launched which can be re-filled by replacement of cartridges. Moreover, the Novolizer\textsuperscript{®} has several other benefits over other DPI devices including a patient feedback mechanism, a trigger flow valve and low to medium intrinsic resistance that ensures that the patient have high flow rates while using this device in comparison to others.\textsuperscript{29} It has been shown that particle size generated by Novolizer\textsuperscript{®} is largely independent of the flow generated by the patient\textsuperscript{30} and tends to have higher drug deposition at higher flow rates.\textsuperscript{31} However, direct head-to-head clinical comparisons among various DPI devices are lacking and preference for a particular may be dictated by physicians and the patient’s preferences considering the costs, design, ease of use, etc.

![Figure 3. Commonly used dry powder inhaler.](image-url)
3. Hold the inhaler level with the mouthpiece and facing down.
4. Tilt your head back slightly, and breathe out slowly and completely without straining or breathing into the device (moisture from breath can clog the inhaler valve).
5. Place teeth over the mouthpiece and seal lips around it making sure not to block the device outlet with tongue.
6. Breathe in quickly and deeply (over two to three seconds) through the mouth to activate the flow of medication.
7. Remove the device from the mouth. Hold breath for 10 seconds (or as long as is comfortable), and then breathe out slowly against pursed lips. This step is very important. It allows the medication to get deeply into the lungs.

**Nebulisers**

Two types of nebulisers are available for use as aerosol generators: jet nebuliser and ultrasonic nebuliser. These work on different principles but have many features in common. These are non-propellant based, do not require patient coordination and can be used to deliver high doses of a particular drug over a short time, such as during acute exacerbations of obstructive airway diseases in emergency settings. Continuous small-volume nebulisation of beta-2 agonists can be employed for patients with acute asthma not responding to intermittent treatment. This method demands more careful monitoring, but supplies higher dosing and more consistent biological levels.

A jet nebuliser works on the Bernoulli’s principle where a high velocity gas (oxygen or air) is passed through a constriction that draws up liquid medication due to the relative vacuum. The result is an aerosol that breaks up into small particles by hitting the inner surface of the chamber. Smaller particles pass through the outlet to the patient whereas larger particles are retained behind in the jet chamber to be re-aerosolised. The size of the aerosol particle is directly proportional to the compressed gas flow and the size of the nozzle. It has been shown that systems that deliver 8 L/min of flow produce ideal-sized particles. Also an intermittent rather than continuous inhalation system leads to lesser loss of medication. The commonly used nebulisers, however, deliver the aerosol continuously.

An ultrasonic nebuliser works by creating a fountain by ultrasonic energy. Aerosol is generated by means of a piezoelectric crystal that functions by converting electrical current into a high frequency vibration. These intense vibrations pass through the drug to be aerosolised and result in formation of droplets. The frequency of vibration determines the size of droplets. Clinical studies have indicated that size of the aerosol particles generated by ultrasonic nebuliser is larger as compared to those from a jet nebuliser. Because of this fact drug deposition in the upper airways may be higher than that with a jet nebuliser.

The major disadvantage of the nebuliser is the cost factor. Equipment is relatively expensive and a lot of drug is wasted. The cost of aerosol therapy is a major concern, as usually patients have to take these medications on a long-term basis. It has been demonstrated that in a controlled setting the efficacy of MDI and nebuliser was comparable for home use as well as for hospitalised patients. Also, the cost of using an MDI is much lower than the nebuliser. Hence, wherever feasible, an MDI should be used, with holding chamber if necessary. However, there are definite clinical situations where use of nebulisers is warranted, such as acute exacerbations managed in emergency and intensive care settings.

**Steps for Ideal Use of Nebulisers**

1. Hands should be washed prior to preparing each nebuliser treatment.
2. If using a multi-dose bottle of medicine, the dropper to put the correct amount of medication into the chamber along with saline solution should be used.
3. The mouthpiece should be connected to the T-shaped part adapter of the chamber.
4. Connect the nebuliser tubing to the port on the compressor.
5. Hold the nebuliser in an upright position to prevent spilling.
6. Turn the compressor on and check the nebuliser for misting.
7. As the mist starts, patients should inhale slowly and deeply through the mouth, taking over three to five seconds for each breath.
8. Hold the breath for up to 10 seconds before exhaling (if possible).
9. Continue until the medicine is finished in the chamber. This may take 5 to 10 minutes.

**CHOICE OF AEROSOL GENERATION DEVICE**

A comparison of the three major aerosol generators is presented in table 2. It is well established that MDI and DPI delivery systems are the most convenient and cost effective and should be the first choice of clinicians for patients with obstructive airway disease. In situations where the patient cannot demonstrate acceptable hand-breath coordination and whenever pharyngeal deposition is a concern such as with inhaled steroids, a valved holding chamber should be used with the MDI. The nebuliser may be used if a high drug dose or large volume is to be given. A nebuliser may also be indicated if the drug is only available as a solution or MDI/DPI are not effective. Patient preference should be
considered when selecting an aerosol delivery device. Many patients might prefer a nebuliser to an MDI or a DPI because of better response, but most of the times it is a consequence of a higher dose being used during nebulisation. In such cases, increasing the total daily dose provided by an MDI or DPI might be useful and may help to convince the patient to continue using the inhalers.

In an evidence-based review by a panel of the American College of Chest Physicians, it was determined that for most patients with asthma, nebulisers, DPIs and MDIs were equally effective in delivering short-acting β₂-agonists, if the device was used appropriately by the patient. Moreover, salbutamol given via an MDI has also been shown to be at least as effective as the nebulised form for the therapy of acute moderate to severe asthma episodes in children.***

**Clinical Uses of Aerosol Therapy**

Majority of drugs available for use as aerosolised medications are used for obstructive airway diseases. Table 3 lists these drugs with their dosages and the type of aerosol generator available with each drug. In addition, a few antibiotics and mucolytic agents are also available for aerosol therapy. Use of inhaled tobramycin is now well established in patients with cystic fibrosis. Many studies have shown improvement in lung function by use of aerosolised tobramycin in patients with cystic fibrosis. This improvement in lung function is attributed to clearing of colonised *Pseudomonas aeruginosa*, which causes recurrent episodes of pneumonia in these patients. Other antibiotics that have been used in aerosolised mode are pentamidine for *Pneumocystis carinii* pneumonia prophylaxis, colistin in cystic fibrosis. amphotericin B

<table>
<thead>
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<th>Table 2. Characteristics of the aerosol generators</th>
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<tr>
<td><strong>MDI</strong></td>
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<tr>
<td>Technique of generation of aerosol</td>
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<tr>
<td>Particle size</td>
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<tr>
<td>Drug deposition</td>
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<tr>
<td>Oro-pharyngeal deposition</td>
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<td>Patient coordination</td>
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<td>Breath hold</td>
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<td>Patient generation of flow</td>
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<td>Amount of drug</td>
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<td>Use for chronic therapy</td>
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<td>Use for emergency management</td>
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<tr>
<td>Use for intubated patients</td>
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<td>Cost</td>
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MDI = metered dose inhaler, DPI = dry powder inhaler

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<tr>
<th>Table 3. Inhaled drugs used for obstructive airway diseases</th>
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<tr>
<td><strong>Drug</strong></td>
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<tr>
<td>Salbutamol</td>
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<td>Salbutamol Sulphate</td>
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<td>Salbutamol Sulphate</td>
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<td>Terbutaline Sulphate</td>
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<td>Terbutaline Sulphate</td>
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<td>Salmeterol Xinafoate</td>
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<td>Salmeterol Xinafoate</td>
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<td>Formoterol Fumarate</td>
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<td>Formoterol Fumarate</td>
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<td>Ipratropium Bromide</td>
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<td>Ipratropium Bromide</td>
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<td>Tiotropium</td>
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<td>Sodium Cromoglycate</td>
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<td>Sodium Cromoglycate</td>
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<td>Beclomethasone Dipropionate</td>
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<td>Beclomethasone Dipropionate</td>
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<td>Budesonide</td>
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<td>Budesonide</td>
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<tr>
<td>Fluticasone propionate</td>
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MDI = metered dose inhaler, DPI = dry powder inhaler
for bronchopulmonary fungal infections in lung transplant recipients and amikacin for E. coli pneumonia. Mucolytics that have been investigated are N-acetyl cysteine, recombinant human deoxyribonuclease and Nacystelyn in cystic fibrosis, and mercapto-ethane sulfonate (Mesna) in patients with COPD.

All the above discussed drugs act through local action in the airways. Recently, a few drugs have been developed or are in the process of development, that are supposed to be delivered through the airways for systemic action. Major steps have been taken in the direction of developing aerosolised insulin that could be used for diabetic patients in place of daily injections. This formulation has been approved in the US and is likely to become available in India in near future. In addition, airways as a route of drug delivery is being explored for many novel therapies including gene therapy, antiproteases and oxidative peptides that may change the paradigm of treatment for many diseases in the years to come.

### AEROSOL THERAPY IN INTUBATED PATIENTS

Intubated patients frequently require aerosolised drugs for various indications and a vast majority of these are bronchodilators. Many patients with obstructive airway diseases require ventilatory support during episodes of exacerbations of their disease. All such patients require inhaled bronchodilator therapy. The mechanics of aerosol therapy are remarkably different in patients who are intubated. This is largely due to the presence of an artificial airway through which aerosol particles have to travel before reaching the lower airways. Aerosol particles have a strong tendency to stick to the walls of the airways and this results in a significant reduction in the fraction of the total drug reaching the lower airways. To avoid this, it has been suggested that the endotracheal tube (ETT) could be bypassed by using a long catheter that attaches to the nozzle of the MDI and release the drug distally in the airways. Other factors that result in poor delivery of the aerosol particles to the lower airways are heating and humidification of the inhaled gas, which results in almost 40% reduction in the fraction of the drug reaching the distal airways. Density of the inhaled gas also affects the delivery because denser gas is more prone to turbulence and this results in higher fraction of drug sticking to the artificial airway. This can be circumvented to some extent by using a less dense gas, such as oxygen and helium. Use of this mixture for ventilation has been shown to improve aerosol delivery. Among the generators, MDI have been found to be more effective than nebulisers. The technique of connecting the generator to ETT is also an important factor that affects the drug delivery. It has been shown that attaching a spacer between the generator and the ETT as well as coordinating the actuation with the inspiration results in a greater delivery of aerosol particles. Several studies have shown that the fraction of delivered dose is almost four times when using a combination of an MDI and a chamber device as compared to that achieved by attaching it directly to the ETT.

### AEROSOL THERAPY IN PEDIATRIC PATIENTS

Aerosol therapy can be effectively given in children of all the ages. As in an adult, aerosol therapy is preferred to systemic administration of bronchodilators and anti-inflammatory drugs. All the methods including nebulisation, MDI, MDI with spacer and DPI are used depending upon the age of the child. For very young children below four years, a spacer is used with face mask (baby maks). Metered dose inhalers use with spacer has been found to be comparable to nebulisers in delivering salbutamol in acute exacerbation of asthma in children. It is very important to select an appropriate device for aerosol therapy that should be given to patients, although there are rough guidelines for choosing the same. These are: (a) children below four years of age, MDI with spacer with face mask; (b) children above four years, MDI with spacer, (c) for children above six years DPI can also be used, and (d) for children above 12 years of age, MDI can be used directly.

### SAFETY OF AEROSOL THERAPY

Although drugs delivered as aerosols have been largely found to be extremely safe, certain clinical situations may require caution on the part of the clinician. Paradoxical bronchospasm is known to occur with DPI formulations of anticholinergic drugs. High doses of β₂-agonists administered through the nebuliser have been reported in rare cases to lead to arrhythmias. Inhaled corticosteroids may have local and systemic adverse effects. Among the local adverse effects oral candidiasis, dysphonia and cough are well known. Incidence of oral candidiasis may vary from 0%-77% depending on the definition used. The data on comparative risk of developing candidiasis with different corticosteroids is conflicting. However, there seems to be a trend towards higher incidence of candidiasis with fluticasone propionate, especially at higher doses, in comparison to budesonide and ciclesonide. Moreover, fluticasone propionate may also result in esophageal candidiasis, again in a dose dependent manner. Incidence of dysphonia is to the tune of 5%-50% and is the result of vocal stress and is again dose dependent. Cough occurs in as many as one-third of patients on inhaled corticosteroids with no difference between different
formulations. The usual interventions aimed at preventing these local adverse effects consist of oral rinse after inhalations, reduction in frequency of inhaled corticosteroids and use of spacer device or holding chamber. Nonetheless, there have been some contradictory results with spacer devices where incidence of cough and dysphonia were noted to be higher with their use. Among the systemic adverse effects, large doses of inhaled corticosteroids may lead to suppression of hypothalamus-pituitary-adrenal axis and must be used cautiously in growing children. A meta-analysis did not find an increase in the risk of loss of bone density and fractures. However, the risk of glaucoma and cataracts tends to increase in patients taking long-term inhaled corticosteroids. Risk of cross-infection with the use of nebuliser in hospital patients is also well known and various methods for decontamination of nebulisers have been described.

CONCLUSIONS

Aerosol therapy has been around for more than 50 years and forms the cornerstone of management of obstructive airway diseases. Recent times have witnessed many advances in this field. Improved aerosol generators with different drug formulations are now available. However, the fraction of total drug eventually delivered to the site of action still remains small. Metered dose inhalers with or without a valved spacer have emerged as the preferred devices for aerosol generation. This holds true for in-hospital patients as well as chronic therapy of patients with obstructive airway diseases. Nebulisers are the generators of choice in an emergency setting. Many new drugs, including insulin, are in the process of development to be used as aerosols that are likely to improve management strategies for various diseases.

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