REVIEW ARTICLE

Therapeutic Aerosol: Principles and Practices

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Summary

Delivering a drug direct to the site of disease has several advantages. In the case of aerosols, it only requires about one-twentieth of the oral dose of the drug to exert its effect, thus resulting in less or minimal systemic side-effects. The onset of action is fast and the efficacy is superior to the oral drug.

Because of the anatomy of the airways which are protective against the inhalation of foreign substances, the aerosol particles must be inhaled in an optimal way in order to reach the sites of action which are the peripheral airways. The particle size must be small and the aerosol must be inhaled in a coordinated manner, especially when a pressurised metered dose inhaler is used.

Because of the high pressure of the propellants used in the canister, the particles will travel at a rapid speed upon actuating, causing great impaction in the throat. Only a small percentage reaches the peripheral airways and this percentage is even smaller if the coordination between actuation and inhalation is poor. Spacers have been shown to be able to overcome this problem of incoordination and to reduce throat impaction. Alternatively, the breath-actuated dry powder inhaler can be effectively used. The nebuliser, which is another aerosol delivery system, needs proper setting of the flow rate of compressed air and an appropriate volume of solution in order to optimise the drug delivery.

Key words: Therapeutic aerosols.

Introduction

Aerosol therapy has been employed in the treatment of respiratory disorders for a long time. It was used during the time of Hippocrates and Galen and continued to be used in India, China and the Middle East for several centuries[1]. It is now the treatment of choice for obstructive airway diseases.

Why Aerosol?

The advantage of aerosol for the therapy of lung diseases lies in its direct action on the diseased site. This allows a smaller dose of drug to be given to the patients, with less side effects but often with better if not comparable therapeutic responses, as compared to oral or parenteral therapy. Inhaled sympathomimetic bronchodilator, for example, provides greater and more rapid bronchodilatation but causes less tremor, tachycardia, palpitation and anxiety, as compared to the oral or parenteral route[2-5]. The dose recommended for metered dose aerosol is usually 20 times less than the oral dose of the same drug[6].

A pharmacokinetic study of inhaled isoprenaline, a bronchodilator drug, has shown that 90% of the inhaled dose is swallowed, but this is deactivated in the gut and liver. Only a small percentage, less than 10%, reaches the lung. Nevertheless, this is the portion that is responsible for its pharmacologic effects[7]. Study with terbutaline suggests that following oral treatment, a plasma level of 4 to 6 ng/ml is needed for optimal bronchodilatation. After the inhalation of the drug, a plasma concentration of 1.5 ng/ml is

achieved, far less than the optimal serum concentration. Despite this, the bronchodilation attained is substantial, suggesting that this is the result of direct action of the drug on the airways[8].

The advantage of aerosol therapy over oral or parenteral therapy for corticosteroid is even more remarkable. Since asthma is a form of inflammatory disease affecting the bronchial tree, anti-inflammatory agents play an important role in the therapy. The most effective and reliable anti-inflammatory agent recognised for asthma management is corticosteroid. Bronchial hyper-reactivity, which is the underlying problem of asthma due to local airway inflammation, has been shown to reduce or reverse with local or systemic corticosteroid therapy[9-12]. However, the systemic side effects, such as Cushingoid appearance, osteoporosis, diabetes, hypertension and infection, pose serious problems and limit the use of systemic corticosteroid. Early attempts at delivering corticosteroid by aerosol were not very successful as the corticosteroid used, dexamethasone, was significantly absorbed in its active form and consequently suppressed the plasma cortisol[13-14]. Newer corticosteroids, like beclomethasone dipropionate and budesonide, when taken orally, are rapidly deactivated principally in the liver, hence systemic availability of active drugs is low[15]. When inhaled, the drugs act locally to control the inflammation in the airways. At the dose of 1000 mcg/day, beclomethasone dipropionate is able to control asthma effectively without significant hypothalamic-pituitary-adrenal suppression[16-19]. The dose of up to 1500 mcg/day may be associated with slight decrease in plasma cortisol — however, the adrenal reserves as assessed by stimulation test with tetracosactrin are still adequate[20-22]. The high dose therapy may help patients who are dependent on oral corticosteroid to either reduce the dose or stop it altogether[23]. This reduces the risk of systemic side-effects substantially. The only side-effects encountered by a few patients are hoarseness of voice and pharyngeal candidiasis, which can be easily overcome by rinsing the throat with water after using the corticosteroid inhaler or by using it with a spacer attachment. If necessary, an oral antifungal agent can be taken.

Inhalation therapy is not only used to deliver bronchodilator drug or corticosteroid, but has also been used to deliver antimicrobial agents to the lung, such as in pneumocystis carinii pneumonia[24] and cystic fibrosis[25] with good effects. Clearly, the advent of aerosol therapy has enhanced our ability to treat various types of respiratory disorders.

Mechanism of Aerosol Deposition

For the aerosolised drug to be effective, it must be able to reach the site of the disease, which is the lung. In the case of asthma, the drug particles must be deposited on the β_2 adrenergic receptors and/or steroid receptors. There are several mechanisms by which inspired particles are deposited onto the wall of the respiratory tract.

Inertial impaction

Inertial impaction occurs when aerosol particles are not able to follow the motion of an accelerated gas in which they are suspended, e.g., in the throat or bifurcation of airways. This is a major particle transport system in the human respiratory tract[26]. Deposition by this mechanism is proportional to the particle velocity and the square of the aerodynamic particle diameter. The larger the size of the particles and the faster the inspiratory flow rate, the greater the impaction. The inertial impaction is important for particles larger than 1 μm in aerodynamic diameter[26-27]. This usually takes place in the first 10 airway generations, at a bend or bifurcation[28].

Gravitational sedimentation

This is the mechanism by which particles are deposited under the action of gravity. Gravitational displacement is proportional to time and square of the aerodynamic particle diameter[26]. The particle deposition in the respiratory tract will be more if the particles are larger, and the longer the aerosol remains

in the lungs. Particles in the 0.5 μm to 5 μm size range may penetrate to the more peripheral parts of the lung and settle on smaller airways either during the breath-holding period or during the course of steady breathing at low frequency[29]. This mechanism occurs usually in the last 5 or 6 airway generations[28].

Brownian diffusion

This is the random motion of particles through uniform, isothermal gas in response to bombardment by gas molecules. It is the major transport system for minute particles, usually less than 0.1 μm in diameter and therefore not very important for therapeutic aerosols, which generally have a diameter larger than 0.5 μm[28]. The deposition is proportional to the square root of time and the square root of the diffusion coefficient of the particles. The smaller the particles and the longer the aerosol remains in the lungs, the larger the deposition by this method.

Electrical transport

Charged particles have been shown experimentally to be deposited more readily than neutral or uncharged particles[30-31]. The contribution to deposition of therapeutic aerosol is thought to be small.

Factors Affecting Aerosol Deposition in the Lung

Since the respiratory tract is made up of many branches, the inhaled particles have a great chance of being deposited in the wall of larger airways, leaving a small proportion penetrating deep in the peripheral airways. Several factors have been identified to further influence the deposition of aerosol in the lung.

Inhalation mode

Certain inhalation manoeuvers have been shown to affect aerosol deposition. When pressurised aerosol was inhaled at 20% vital capacity, Newman *et al*[32] showed a significantly greater lung deposition when compared to inhalation at 50% or 80% vital capacity. Dolovich *et al*[33], however, did not see any difference in the lung deposition of radiolabelled aerosol when actuated at different lung volumes. Newman *et al*, in the same study, had also shown that holding the breath for 10 seconds at the end of inhalation resulted in larger deposition of aerosol in the lung, as compared to breath-holding for 4 seconds. This effect was only seen when pressurised aerosol was actuated at 50% and 80% vital capacity, but not at 20% vital capacity. Both Newman *et al* and Dolovich *et al* showed that slow flow rate of inhalation of less than 1.0 litre/second improved the lung deposition. Williams, however, did not find any significant difference in lung function response to inhalation of pressurised aerosol at 0.5 litre/second and 2.0 litre/second[34]. Placing the actuator away from mouth had been shown to result in a larger deposition of pressurised aerosol in the lung as compared to placing it close to the mouth[33]. In conclusion, evidence suggests that actuating the inhaler at the beginning of slow inhalation, followed by holding the breath for some duration, may optimise the deposition of pressurised particles within the lung, although some investigators did not find any therapeutic advantage of such a proposition.

Nature of particles

Deposition of particles in the respiratory tact may be influenced by the property of the particles such as the size, shape and hygroscopicity. Size of the particles is perhaps the most important factor. Particles of larger than 12 μm may not penetrate the alveolar region at all, whereas particles of 0.5 to 5 μm may have the best chance of being deposited in the lung by inertial transport and gravitational sedimentation. Particles of 2 μm or less had been shown to be better deposited in the peripheral airways than the larger particles[35-36]. The lung function improved to a greater degree in asthmatics who inhaled the bronchodilator drug of smaller than larger particles[37]. The shape of particles is also important. Asbestos fibres of 20 μm long and 0.5 um wide may be found in peripheral airways and lung parenchyma[38].

Hygroscopicity is the property of particles to absorb water. Water soluble particles may absorb water in humid atmosphere of respiratory tract and enlarge their sizes[39]. This effect is, however, difficult to study in humans.

The state of the airways

The anatomy of airways between individuals differs considerably and may affect the deposition of particles[40]. Airway narrowing due to various diseases may also cause lower aerosol deposition[41].

Types of Therapeutic Aerosol Delivery Systems

There are essentially 3 types of aerosol delivery systems used in clinical practice, namely, the pressurised metered dose inhaler (MDI), the dry powder inhaler (DPI) and the nebuliser.

Metered dose inhaler

The metered dose inhaler is a system whereby drug particles are either suspended or dissolved in chlorofluorocarbon propellants at a high pressure[42]. In a suspension aerosol, fine drug particles are suspended with a surfactant in chlorofluorocarbon (freon) propellants. The surfactant prevents the agglomeration of the drug particles so that the tiny size is maintained within respirable range. Sorbitan trioleate, oleic acid or lecithin are among the commonly used surfactants[43]. In a solution aerosol, the active drug, propellants and ethyl alcohol co-solvent are mixed homogeneously in a canister. The high vapour pressure of around 400 kPa keeps the propellants in the liquid phase within the canister. Fig 1 shows the diagram of a typical inhaler. A canister is mounted in a plastic actuator. At the bottom of the canister there is a small metering chamber (25 µl to 50 µl volume), which is normally open to the rest of the canister. This metering chamber will be closed to the rest of the canister but open to the atmosphere when the canister is pressed down into the actuator. This will release the contents of the metering chamber in the form of splashed droplets which will travel at a high velocity due to the high pressure of propellants.

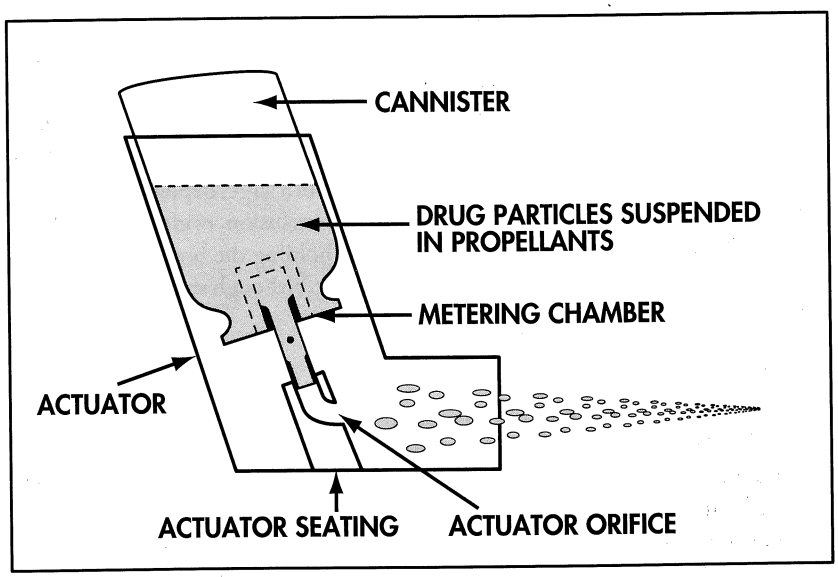

Fig 1: A diagrammatic representation of a pressurised metered dose inhaler.

The propellants evaporate as they travel. At the actuator orifice, the droplets have a mass median diameter (MMD) of 43 μm and the size falls to 14 μm at 10 cm[44]. After complete evaporation of propellants, the aerosol has a MMD of 2.8 μm to 4.3 μm and geometric standard deviation (GSD) of 1.5 μm to 2.1 μm[45]. This size range of particles is regarded as optimal for peripheral lung deposition. The speed of the droplets also varies, being fastest immediately after the release (about 100 km/h) and decreasing in speed as they travel against the resistance of the air[46]. These 2 factors of changing particle size and high velocity are important in causing high throat impaction, especially if the coordination between actuation and inhalation is poor. The spacer, which is a tube placed between the actuator and the mouth, is designed to overcome these 2 factors, so that the aerosols will be allowed to reduce their speed and evaporate to smaller sizes before they are inhaled. This subject will be discussed in greater detail below. Despite good actuation-inhalation coordination, the percentage of pressurised particles deposit within the lung is small, between 8% to 16%[7, 47-50].

Several steps are recommended by most of the drug manufacturers and some investigators, to optimise the inhaler use, which usually include:

1. Shaking the canister.
2. Holding the canister upright.
3. Breathing out fully.
4. Placing the inhaler mouth-piece between the lips.
5. Actuating the inhaler while breathing in slowly and deeply.
6. Holding the breath for 10 seconds or for as long as possible.
7. If the dose is to be repeated, waiting at least 1 minute.

Although most steps are simple, step 5 clearly needs good coordination and may prove to be difficult for some patients. This has been observed by several investigators who reported between 14% to 90% of faulty technique among patients[51-53]. Elderly patients, young children and patients with joint or limb deformity or arthritis may find that all the steps for correct inhaler use are far too difficult. For most patients, changing to dry powder inhaler will solve the problem, but not for patients with deformities or arthritis.

Dry powder

Dry powder is a system whereby drug particles are inhaled directly from an inhaler device without having to be suspended in propellants. The drug particles of less than 3 μm in gelatin capsules need to be broken or punctured for the inhalation[54]. It is a breath-actuated system in which the delivery of drug powder occurs only with each inhalation. Because of the small particles used, the capsules may be inefficiently emptied, thus larger particles (30 μm to 70 μm) served as carriers are added to the drugs to improve emptying. The carrier powder is usually made of lactose or glucose. The earlier 2 systems available are Spinhaler, for the delivery of sodium cromoglycate, and Rotahaler, for salbutamol and beclomethasone dipropionate. The *in vitro* assessment of the Rotahaler suggests that the larger carrier powder will be mainly impacted in the throat and the smaller drug particles will be deposited deeper in the respiratory tract[55].

Pharmacokinetic study suggests that less than 4% of disodium cromoglycate powder is deposited within the lung when inhaled from a Spinhaler[7]. Study with radiolabelled aerosol shows that about 9% and 14% of the dose inhaled, from a Rotahaler and Turbuhaler respectively, is deposited within the lung[56-57]. Studies

with bronchodilators and corticosteroids have shown that dry powder inhaler is as effective as metered dose inhaler[58-63]. Patients who had difficulty in using the pressurised metered dose inhaler have been shown to be able to use the dry powder inhaler well[64] and younger children have benefitted more from this system[65].

Nebuliser

The nebuliser is a type of inhalation device that generates aerosol from its solution. There are 2 types of nebulisers used in practice, namely, jet nebuliser and ultrasonic nebuliser. Jet or pneumatic nebuliser uses compressed air or oxygen, either from a cylinder or a compressor, to generate aerosol droplets by Venturi action. Ultrasonic nebuliser generates aerosol by high frequency vibration produced by an electronic oscillator.

The setting of the correct flow rate is crucial for the jet nebuliser, and the size of the aerosol is inversely proportional to the flow rate of the compressed air[66]. For ultrasonic nebulisers, the particle sizes vary inversely with the two thirds power of the acoustic frequency[67]. The small particles with diameter of less than 5 μm are optimal for peripheral lung deposition and ought to be achieved by nebulisers. Clay *et al*[68] has shown that when a high flow rate of compressed air was used to generate terbutaline particles of 1.8 μm diameter, the bronchodilator responses were better than after inhaling larger particles produced by a lower flow rate of compressed air. Douglas *et al*[69], however, did not observe any significant difference in FEV_1 response when nebulised bronchodilator drug particles of 4 μm were compared with 11 μm. The setting of flow rates is also important in determining the nebuliser output and the duration of nebulisation. The higher the flow rate, the faster the solution is nebulised[70]. The total volume of the nebuliser solution will also affect the nebulisation time, being longer with the larger volume. The proportion of the drug that is nebulised is, however, more with the larger volume of the solution. Generally, the flow rate of 8 litres/min and the total volume of 3 ml to 4 ml is regarded as optimal.

The amount of drug deposited in the lung when inhaled from the nebuliser varies between studies. Admundsson *et al* found that only 1% to 2% of the original dose used in the nebuliser was detected in the lung[71]. Ruffin *et al*[72], found up to 10% lung deposition when the nebuliser was used with intermittent positive pressure breathing (IPPB). Zainudin *et al*[56] and Lewis and Fleming[73], detected about 10% to 12% of the original nebuliser dose in the lung when the jet nebuliser was used. The rest of the drug was found in the instrument or expired air. The nebulised aerosol did not seem to be affected by different breathing manoeuvers and breathing at tidal volume is effective[74].

Spacer devices

The spacer is a tube or chamber device placed between the pressurised canister and the patient's mouth, for use with a metered dose inhaler. It is designed to allow the rapidly moving droplets to slow down and evaporate to a smaller size, rendering them more suitable for inhalation and lung deposition. Spacers may come in the tube shape of 10 cm long, cone or pear shape of 750 ml volume or collapsible chamber with a reed device to indicate the flow rate of inhalation. Studies with spacers have shown mixed results, with some showing therapeutic advantages over MDI alone[75-77], while others show no difference in bronchodilator responses[78-80]. Using radiolabelled aerosol, Newman *et al*[81] showed a greater lung deposition of aerosol with less oropharyngeal deposition when the spacer was used with MDI. This may reduce the local side-effects such as dysphonia and pharyngeal candidiasis when used with a corticosteroid pressurised inhaler. Coordination between actuation and inhalation seems to be less crucial when MDI is used with a cone or pear-shaped spacer, as the aerosol is suspended within the spacer and can still be effectively inhaled after a slight delay[82]. The spacer, therefore, serves as an alternative for patients who have difficulty in using the conventional metered dose inhaler.

Future of Therapeutic Aerosol and Malaysian Scenario

There is more than sufficient evidence to support the use of aerosols for the treatment of various respiratory diseases, especially airway obstruction. The type of aerosol used may change, with a greater tendency towards using chlorofluorocarbon (CFC) free aerosol in view of its effect on the environment, i.e., ozone depletion and the consequent risk of skin cancer[83]. For this purpose, unless a CFC-free propellant is found, the only way out is to use the dry powder inhaler. There is enough proof to support the use of the dry powder inhaler, which is undoubtedly effective and most probably equipotent when compared to the metered dose inhaler. The newer dry powder inhalers, like the Turbuhaler[57] and Diskhaler[84], are also convenient and handy, as multiple doses can be loaded. Other developments in the future will be the use of longer-acting bronchodilator drugs in the dry powder and a potent topical steroid completely free from systemic side-effects. Aerosols may also be used more widely for the treatment of respiratory tract infections, including fungal pneumonia.

In Malaysia, the inhalers have been available for almost 2 decades. Their use was initially limited, but has become more widespread recently, both in government hospitals and private practice. The cost of the inhaler, rather than the adverse effects, was the reason why it was slow in gaining popularity among doctors. This was especially so in government hospitals. Despite the safety record of modern inhalers, only specialists or consultants were allowed to prescribe the inhalers in the 1980s. The policy has, however, changed recently, and medical officers are now allowed to prescribe bronchodilator inhalers, although the prescription of corticosteroid inhalers must be supervised by a specialist or consultant.

Superficially, it appears that the bronchodilator inhaler is 2 to 3 times more expensive, dose for dose, than the oral bronchodilator (Table I). Since the management of asthma is more towards early use of inhaled corticosteroid on a regular basis to dampen the inflammation, the usage of inhaled bronchodilator will be reduced in the long run, as it is used only for symptom relief rather than regularly. This is, however, parallel with the increased use of inhaled corticosteroid and the cost incurred. Although the direct impact, especially to the government, is more spending incurred on drugs, this may be compensated by less expenditure on in-patient care for acute asthma, as the admission rate is expected to be reduced with better care of the disease.

Table I
The prices — for government hospitals — of oral and inhaled bronchodilator and inhaled corticosteroid per dose
Source: Hospital Besar, Kuala Lumpur

Drug		Price per tablet or puff
Salbutamol tablet	(2 mg)	0.4 cent
Terbutaline tablet	(2.5 mg)	1.1 cent
Neulin tablet	(125 mg)	0.9 cent
Neulin SR	(250 mg)	16 cent
Salbutamol inhaler	(100 mcg)	1.5 cent
Terbutaline inhaler	(250 mcg)	2.3 cent
Beclomethasone inhaler	(50 mcg)	2.5 cent
Beclomethasone inhaler	(250 mcg)	24.0 cent
Budesonide inhaler	(200 mcg)	23.0 cent

The scenario in private practice is slightly different. Oral bronchodilators are used widely by private practitioners. The main reason is likely to be the lower price of oral drugs as compared to inhalers, although ignorance of the current trends of management is also a possibility. Doctors may choose to prescribe a cheaper drug than a more expensive but appropriate one so that the patients' bills are not exorbitant. This attitude is certainly not correct, as the patients may suffer recurrent symptoms which might affect their well-being, income and at times, their lives. For the management of moderate to severe asthma, there is no justification whatsoever for the use of prednisolone on a long-term basis without first treating the patients with inhaled corticosteroid, which has negligible side-effects. In this respect, cost should not be the reason for not prescribing the inhalers.

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