Principles of Aerosol Therapy

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Aerosols are increasingly recognized as the mainstay of maintenance therapy of reversible airways obstruction. This is because of their high bioavailability resulting from topical administration to their site of action in the airways and minimal side effects resulting from the relatively small therapeutic dose requirements.1,2 Aerosolized adrenergic bronchodilator drugs have been shown to be more effective in the management of asthma than intravenously administered sympathomimetic medications, not only in terms of bronchodilator response,3 but also because the latter can result in unacceptable side effects before maximum bronchodilatation has been achieved.4 Similarly, terbutaline aerosol was shown more effective than systemically administered drugs for preventing exercise or cold-induced asthma,5,6 while nebulized salbutamol was much more effective than the oral form for preventing histamine-induced bronchospasm.6,7

SITE OF ACTION

There has been some dispute about the site of action of bronchodilator aerosols. It has been suggested that much of the effect results from absorption of the inhaled adrenergic agonist followed by blood-borne delivery to airway smooth muscle.8 Recent carefully performed placebo-controlled randomized double blind studies suggest, however, that significant bronchodilatation following adrenergic aerosol inhalation results entirely from the relatively small dose of aerosol that is delivered to the lower respiratory tract. Ruffin et al.9 in a dose-response study, demonstrated that approximately 30 μg of aerosolized fenoterol delivered to the lower respiratory tract was sufficient to produce maximum bronchodilatation. In a separate study, these same investigators comparing bronchodilator effect of 200 μg of fenoterol inhaled from a metered-dose inhaler with 500 μg gargled and swallowed showed that whereas the aerosol route produced effective bronchodilatation, the gargled and swallowed material was ineffective compared with the placebo control.10 More recently, Newman et al.11 compared the bronchodilator effect of nebulized terbutaline delivered at total lung capacity with the same drug inhaled at various lung volumes between residual volume and 20 percent below total lung capacity (TLC). They showed that no bronchodilator effect resulted from TLC delivery of aerosol, whereas drug inhaled at any of the other lung volumes produced effective and similar bronchodilatation.

SITE OF DEPOSITION

The optimum site of deposition of bronchodilator drugs in the lower respiratory tract has not been fully established. However, evidence from animal studies,12 and in man,13 suggests that beta-adrenergic receptors are located throughout the respiratory tract. This provides the basis for attempting to achieve the most even possible intrapulmonary deposition of such inhaled bronchodilator agents.

The site of deposition of inhaled aerosols depends upon particle related factors such as particle size, shape, density and whether the aerosol is heterodisperse, that is, containing a wide range of particle sizes, or monodisperse, containing particles of uniform size. A heterodisperse aerosol is characterized by its mass median aerodynamic diameter (MMAD) and has a geometric standard deviation greater than 1.2. Recent studies14 have indicated that the aerodynamic behavior in the lung, of a heterodisperse aerosol of a given MMAD, will vary by no more than 10 percent from that of a monodisperse aerosol of similar MMAD. Thus, for clinical purposes there would appear to be no advantage to generating monodisperse aerosols which are much more difficult to produce and currently are best suited only to research studies in well equipped aerosol laboratories.

FACTORS DETERMINING DEPOSITION

For aerosols in the therapeutic range of 1-10 μm, airway and airflow-related factors are as important or more important than the MMAD of the aerosol in determining the site of deposition.15 These include, in order of importance, (1) inspiratory flow rate, (2) inspiratory time or frequency of breathing, as well as breath-holding time, and (3) tidal volume. In patients with pulmonary disease, a reduction in airway caliber resulting from bronchoconstriction, mucosal edema, mucus plugging and pathologic alterations in the airways or lung parenchyma may be of over-riding importance.16,17

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for the deposition of particles between 3 and 10 μm, particularly at high inspiratory flow rates. Such particles are deposited in the proximal airways of the nose, pharynx, larynx and the proximal tracheobronchial tree as a result of inertial forces. Particles between 3 and 1 μm are deposited with increasing efficiency in intermediate and smaller airways from approximately the 6th to 17th bronchial division due mainly to sedimentation due to gravitational forces. Particles below 0.1 μm are deposited fairly uniformly throughout the respiratory tract by diffusion. The particle size range between 1 and 0.1 μm is of considerable interest because such particles are too large to diffuse significantly, but too small to be deposited efficiently by gravitational forces. They thus remain suspended in the airstream and approximately 80 percent are exhaled. The early promise that such small particles might be particularly useful as bronchodilators has not been borne out by recent preliminary studies in patients with mild to moderate asthma. Nevertheless, they do have the potential for achieving more peripheral airways and might find a use in the management of patients having a component of reversible airways obstruction superimposed upon mainly fixed chronic obstructive disease.

**Optimum Delivery**

A major problem of aerosol therapy relates to the difficulty that many patients have co-ordinating inhalation and aerosol delivery from metered dose inhalers. On theoretical grounds, optimum delivery should be achieved by using aerosol particles of 1-3 μm inhaled at low inspiratory flow rates from approximately functional residual capacity (FRC) to TLC. Retention of the aerosol in the lung can be enhanced by prolonged breath-holding. In initial clinical studies, Ryan et al demonstrated that at an inspiratory flow rate of approximately 2 Lps, only one fifth of the dose of aerosol was deposited in the lower respiratory tract compared to that when flow rates were between 0.5 and 1 Lps. Subsequent studies using labelled solution aerosol delivered from a metered-dose inhaler evaluated the effect of inspiratory flow rate, lung volume from which the aerosol bolus was inhaled, and whether the metered-dose inhaler was held in the close lips, at the lips with mouth open and 2 or 4 cm from the open mouth. The breath-holding time, previously shown by Pavia et al to be optimum at 10 sec, was held constant. These studies in 12 normal subjects showed that a maximum of 12 percent of the aerosol produced by the MDI achieved the lower respiratory tract when the aerosol bolus was inhaled from FRC at less than 1 Lps with the MDI mouthpiece held 4 cm from the wide open mouth. Clinical studies in asthmatic subjects have demonstrated that maximum bronchodilatation is achieved under similar circumstances.

**Delivery Devices**

To overcome coordination problems which beset many patients, particularly the elderly, physically or mentally handicapped or children, various devices have been developed to assure optimum aerosol therapy. Such devices have included pressure driven nebulizers, ultrasonic generators, intermittent positive pressure breathing devices, and simple tubes or valved holding chambers, all of which are designed to provide aerosol on inhalation and minimize coordination problems which may lead to failure of aerosol therapy.

The ideal aerosol delivery device should be portable, inexpensive, signal aerosol delivery, provide selective lower respiratory tract aerosol delivery while minimizing delivery in the upper respiratory tract, and should be readily used by children as well as the aged and handicapped. In an attempt to fulfill these requirements, a valved holding chamber (Aerochamber), was developed in our laboratory. It consists of a rigid plastic cylinder approximately 11 x 4 cm with an adapter at one end allowing insertion of the mouthpiece of any standard MDI, while at the other end, there is a valved mouthpiece which allows the patient to breathe aerosol from the chamber after the metered dose of aerosol has been discharged into it. On exhalation, the closed valve prevents breathing into the holding chamber as exhaled air enters the room. This simple system obviates the need for hand-lung coordination during aerosol delivery and assures breath-actuated aerosol inhalation with a minimum of instruction. Labelled aerosol studies have demonstrated similar pulmonary aerosol deposition in normal subjects and patients with obstructive airway disease when the MDI is used together with an Aerochamber compared with MDI alone. However, upper airway deposition of aerosol is decreased approximately 15-fold when the Aerochamber is attached. Clinical studies in children and adults have shown similar bronchodilatation when aerosol is inhaled by means of the Aerochamber as compared with physician-administered MDI alone. The advantage of a decreased upper airway aerosol dose has been demonstrated in studies which showed a significant reduction in dysphonia and thrush in patients inhaling steroid aerosols from this device.

In recent years, there has developed a greatly improved understanding of aerosol physics, aerosol delivery to the respiratory tract and therapy of asthma. Aerosols are now considered by many clinicians to provide the basis for the maintenance therapy of patients with reversible airways obstruction by means of sympathomimetic and anticholinergic drugs and steroids, as well as drugs such as cromolyn sodium (Intal). Recent studies of aerosol deposition from MDI
units have provided a basis for optimizing aerosol delivery in patients who can be readily instructed in their use. Furthermore, simple add-on devices have been developed for the approximately 20 percent of patients who find inhalation from metered dose inhalers difficult, thus most patients, including infants, can now be effectively treated with aerosols.

SUMMARY

Aerosol therapy with a variety of drugs is superior to oral and, except perhaps in status asthmaticus, parenteral therapy. An understanding of aerosol physics and the physiologic characteristics relating to ventilation allows optimum aerosol delivery for maximum benefit in the majority of patients. In those patients who are unable to use metered-dose inhalers effectively, simple inhalation devices have been developed which assure breath-actuated aerosol delivery to the lower respiratory tract with minimal side effects.

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