Aerosol Therapy of Bronchial Asthma*

Michael T. Newhouse, M.D., M.Sc.
Myrna Dolovich P. Eng.

Therapeutic utopia is surely characterised by effective treatment with little or no side-effects. In the management of reversible airflow obstruction, aerosols come closest to fulfiling this ideal. Thus, in most parts of the world, aerosols have become firstline therapy for the management of asthma and chronic airflow limitation with a reversible component of airflow obstruction.[1,2]

Recent studies have also suggested that aerosols might be useful for treating RSV and influenza B infections involving the respiratory tract,[3,4] and in the management of bacterial infections in patients with cystic fibrosis.[5,6] Non-respiratory applications such as the treatment of migraine with aerosolised ergotamine[7] have also been investigated.

Aerosol therapy is not new. For over a century, smoke from *Atropa belladonna* and *Datura stramonium* leaves was inhaled to provide relief from attacks of asthma.[8] However, it is only in recent years that close collaboration among chest physicians, pharmacologists, engineers and aerosol physicists has succeeded in putting aerosol therapy on a sound scientific basis.

The major advantage of aerosols lies in their surface application to the airway, where minute doses of the therapeutic agent provide potent topical activity, usually with minimal systemic effects.[9,10] Thus, in contrast to systemic therapy, aerosols can provide maximum bronchodilatation with little or no attendant side-effects of tremor, tachycardia, arrhythmia and anxiety.[11] In asthmatics, adrenoceptor agonist aerosols are more effective than the oral form in protecting against exercise-induced asthma,[12] in decreasing airway reactivity[13] and in providing better bronchodilatation with less tremor than intravenous therapy.[14,15] Similarly, topical steroids can be used for asthma prophylaxis without the unsightly and often life-threatening complications associated with iatrogenic Cushing's syndrome. Table 1 lists some of the drugs that are delivered as aerosols.

Table 1

Bronchodilators	Anti-inflammatory	Antibiotics
Adrenoceptor agonists	– sodium cromoglycate	– carbenicillin
– fenoteral	– beclomethasone dipropionate	– ticarcillin
– Salbutamol	– budesonide	– tobramycin
– terbutaline	– triamcinolone acetate	– gentamicin
– isoproterenol		– ribavirin
Anticholinergics		
– ipratropium bromide		
– atropine methonitrate		

Aerosol physics

If aerosols are to be used optimally, it is essential to have some understanding of the physics of aerosols, particularly the relationship between aerosol particle size and airway deposition. An appreciation of the significance of changes in airflow characteristics and airway calibre in determining the distribution of aerosols in the airway is helpful when considering delivery of an effective bronchodilator dose.[16,17]

The two parameters that characterise an aerosol are its mass median aerodynamic diameter (MMAD) and the geometric standard deviation which is an indication of the dispersion of particle diameters within the aerosol. Aerosols generated by various nebulisers or metered dose inhalers produce particles with a size range of 0.5-35 micrometres (μm),[18] but only a small fraction of the aerosol, mainly that between 1-5 μm, is deposit-

*From the Firestone Regional Chest and Allergy Unit, St. Joseph's Hospital, McMaster University, Hamilton, Ontario, Canada.

ed in the lower respiratory tract.[19] Under optimum conditions, only about 10-12 per cent of the output from an MDI and 1-5 per cent of that from most jet or ultrasonic nebulisers is actually deposited in the pulmonary airways. Despite the inefficiency of aerosol systems, minute but highly effective doses of medication are deposited onto the respiratory tract mucosa.[20] Thus, we may well ask why aerosol delivery systems are so inefficient.

The answer to this lies in aerosol physics and in the behaviour of the bronchial tree as an efficient aerodynamic filter. Aerosols in the 1-5 μm particle size range are useful therapeutically because such particles effectively penetrate the filter and are deposited in the lower respiratory tract.[21]

Aerosol particles are deposited in the lung according to three main physical principles:[22] 1. *Impaction,* resulting from inertial forces acting chiefly on particles over 5 μm causing them to deposit in the nose, pharynx and larynx as well as on the first few bronchial divisions. This effect is more marked at high inspiratory flow rates and in patients with airflow obstruction due to a reduction in airway calibre. 2. *Sedimentation.* Smaller particles, in the size range of 5-1 μm, are deposited mainly by sedimentation resulting from gravitational forces. Such particles can penetrate effectively into peripheral airways because their inertia is low and they are not efficiently trapped in the aerodynamic filter of the upper airways. 3. *Diffusion.* Submicronic particles, particularly those below 0.1 μm in size, are deposited by Brownian forces (diffusion) and the deposition efficiency increases with decreasing particle size. Since the mass of such small particles is very low, it is unlikely that their therapeutic potential is great although this has not been well explored.

Thus, aerosols intended for nasal deposition should have a coarser particle size for improved deposition by impaction, while those aerosols designed to go into the lower respiratory tract should be finer to minimise upper airway deposition and encourage deeper penetration into the lung.

Of almost equal importance to particle size in determining aerosol deposition in the airway are the respiratory variables: inspiratory flow rate, frequency and tidal volume,[23,24] while pathological abnormalities, particularly airway narrowing, also exert an effect on aerosol retention and penetration into the airway.[17,25] It is the inspiratory flow rate which provides the energy to carry an aerosol into the lung; the greater the flow rate, the greater the particle inertia and the amount of aerosol deposited by impaction. Thus, at high flow rates (> 1 L/sec), therapeutic aerosols (MMAD 1-5 μm) are increasingly deposited in the more proximal airways.

Only particles that impinge on the airway wall have therapeutic potential and since a finite period is required for therapeutic aerosol particles to reach the mucosal surface (sedimentation rate of 3 μm particles = 0.3 mm/sec), the respiratory frequency (breath-holding time) is an important determinant of therapeutic reponse.[26] Tidal volume is less important and breaths greater than 2-3 times the dead-space appear to have relatively little additional effect on aerosol distribution or bronchodilator response.[27]

In patients with severe airflow obstruction, it has been shown that the penetration of aerosols into peripheral airways, where the largest number of beta receptors lie, is greatly decreased and most of the inhaled dose is deposited centrally.[17,25,28] It is largely for this reason that much larger doses of bronchodilators need to be used during episodes of life-threatening asthma.[29] This is particularly true if nebulisers rather than MDIs are used for aerosol delivery because nebulisers are only 10-30 per cent as efficient as MDIs.[18,30] Thus, as the standard dose of nebulised bronchodilator is 2.5-5 mg of salbutamol or fenoterol with 5 per cent actually delivered to the lung, if pressurised aerosols are used in severe asthma, the MDI-delivered medication need only be 25-50 per cent of the nebulised dose to achieve equivalent bronchodilator response (i.e. 6-12 puffs at 100 μg/puff).[30]

Aerosol generation

Therapeutic aerosols are generated via a) metered dose inhalers providing fluorocarbon-propelled aerosols or dry powder aerosols, b) ultrasonic or jet nebulisers producing aerosol droplets which patients inhale by negative pressure breathing or, c) intermittent positive pressure devices providing aerosols from jet or ultrasonic nebulisers by means of positive pressure.

The choice of delivery system is chiefly a question of convenience, cost and technical difficulty since none of the more costly and complicated methods for delivering aerosol has been shown to have any theoretical or practical advantage over the technically sophisticated but cheap and convenient metered dose inhaler. Currently, aerosol therapy with compressor or compressed gas cylinder-driven nebulisers is usually reserved for patients unable or unwilling to use metered dose inhalers. Evidence accumulated during the past 10 years,[31,32] including a recent multi-centre trial in the United States involving 1,000 patients studied for nearly three years, has demonstrated conclusively that there is no advantage to long-term IPPB aerosol delivery.[33] A possible exception is the treatment of croup with epinephrine[34] or laryngeal candidiasis (thrush) with mycostatin,[35] where one can take advantage of the high inspiratory flow rates provided by IPPB to increase delivery of these drugs to the larynx.[16] It is worth emphasising that there is no scientific basis for the practice of providing IPPB bronchodilator aerosols to

outpatients three or four times a week.

Aerosol delivery

In recent years, aerosols delivered from metered dose inhalers have been shown to be as effective as from other aerosol delivery systems,[30,36] even in patients with life-threatening asthma, provided the bronchodilator dose is appropriately augmented (three- to six-fold).[36] Equally reliable MDI delivery can be achieved using one of the newer valved aerosol-holding chamber systems attached to the MDI.[30,37-39] With increasing emphasis on cost control in North American hospitals, this approach to aerosol therapy is gaining increasing support as the cost is approximately 50 per cent less than that for nebuliser-delivered bronchodilator solutions.[40] A further important consideration is that aerosol-borne nosocomial infections are virtually eliminated with the use of the MDI.[41]

In daily practice, approximately 15 per cent of patients with asthma and chronic airflow limitation are unable to use metered dose inhalers because of poor hand-breath coordination and handicaps such as rheumatoid arthritis or stroke.[42,43] The elderly and children under five can likewise have difficulty operating an MDI.[44] MDIs attached to valved holding chambers can assure aerosol delivery in such patients, decrease cough during aerosol inhalation in patients with marked airway hyperreactivity and reduce or eliminate thrush and hoarseness in patients on steroid aerosols.[45]

There is still some dispute about the optimum way of using metered dose inhalers. Some physicians and most drug companies advocate placing the actuator mouthpiece of the metered dose inhaler between the closed lips and then breathing in more or less rapidly from an unspecified expiratory volume to total lung capacity. Based on recent studies in our laboratory[46] and by others,[47,48] the MDI technique outlined in Table 2 is suggested for those patients who demonstrate good hand-breath coordination.

Table 2 Optimal MDI aerosol administration technique.

1. Remove MDI cap.
2. Shake.
3. Hold actuator mouthpiece 4 cm (two finger widths) in front of the widely opened mouth.
4. Breathe out to resting end expiration (functional residual capacity).
5. Initiate a slow inspiration to total lung capacity (which should take approximately five seconds).
6. At TLC, hold breath for 5-10 seconds.
7. Repeat this manoeuvre as many times as necessary to deliver the number of puffs prescribed.

Approach to therapy

When long-term inhaled steroid therapy is initiated, a short course of oral steroids is given simultaneously and then is rapidly reduced after 7-10 days. To improve patient compliance, the therapeutic programme should be made as simple and easy to follow as possible. Thus, we do not normally ask patients to wait five or 10 minutes between adrenoceptor aerosol puffs even though this has been shown to produce somewhat better bronchodilatation,[49] but we do recommend that they wait five minutes between the application of their bronchlodilator and steroid aerosol in the expectation that penetration of the latter into more peripheral airways will be augmented. A further recommendation is that the total daily steroid aerosol dose be divided into two and taken on arising in the morning and at bedtime.[50,51] For more severe asthmatics, the use of bronchodilators is recommended four to six times daily, although patients well controlled on a daily prophylactic regimen may do well with adrenoceptor agonist therapy only when needed. In cold air and exercise-induced asthma, adrenoceptor agonist aerosols administered five minutes before activity will often prevent attacks, but if protection is incomplete, the addition of 2-4 puffs of sodium cromoglycate along with adrenoceptor agonists is usually effective.[52]

The use of anti-cholinergic bronchodilator therapy for treating asthma has been known for several hundred years. Recently, ipratropium bromide has become available and has been found particularly useful in the treatment of chronic airflow limitation, for which it has been shown to be more effective than adrenoceptor agonists.[53] This drug may also be effective in the treatment of vasomotor rhinitis[54] and rhinorrhoea during the first few days of the common cold.[55,56]

It is clear that aerosol therapy is now well established in the management of reversible airflow obstruction and has potential value in the management of respiratory tract infections as well. But this is only the beginning. In the offing are improved steroid aerosols, more effective adenosine antagonists than theophylline, antagonists of the leukotrienes and of leukotriene synthesis, and perhaps also more bronchial smooth muscle-specific calcium channel blockers. Many of these will likely become available in the next few years in aerosol form further to improve our understanding of asthma mechanisms and management, particularly in those cases that are still resistant to currently available therapy.

REFERENCES

1. Clark TJH. Factors influencing route of administration of airway therapy. In: Sadoul P, Milic-Emili J, Simonsson BG, Clark TJH, eds, Small airways in health and disease. Amsterdam: Excerpta Medica, 1979:170-8.
2. Dolovich J, Hargreave FE, Wilson WM, Greenbaum J, Powles ACP, Newhouse MT. Control of asthma. CMA Journal 1982; 126:613-8.
3. Hall CB, McBride JT, Walsh EE, *et al.* Aerosolized ribavirin treatment of infants with respiratory syncytial viral infections. N Engl J Med 1983; 308:1443-7.
4. Wilson SZ, Gilbert EE, Quarles JM, *et al.* Treatment of influenza A (H1N1) virus infection with ribavirin aerosol. Antimicrob Agents Chemother 1984; 26:200-3.
5. Hodson ME, Penketh ARL, Batten JC. Aerosol carbenicillin treatment of pseudomonas infection in patients with cystic fibrosis. Lancet 1981; 2:1137-9.
6. Kun P, Landeau LI, Phalan PD. Nebulized gentamycin in children and adolescents with cystic fibrosis. Aust Paediatr J 1984; 20:43-5.
7. Crooks J, Stephen SA, Brass W. Clinical trial of inhaled ergotamine tartrate in migraine. Brit Med J 1964; 1:221-4.
8. Cooper S. A dissertation on the properties and effects of the datura stramonium or common thorn apple. Philadelphia: Smith, 1797:1539.
9. Larsson S, Svedmyr N. Bronchodilating effect and side effects of beta$_2$-adrenoreceptor stimulants by different modes of administration (tablets, metered aerosols and combinations thereof). Am Rev Respir Dis 1977; 116:861-9.
10. Shim C, Williams MH Jr. Bronchial response to oral versus aerosol metaproterenol in asthma. Ann Intern Med 1980; 93:428-31.
11. Rossing TH, Fanta CH, Goldstein DH, *et al.* Emergency therapy of asthma: comparison of the acute effects of parenteral and inhaled sympathomimetics and infused aminophylline. Am Rev Resp Dis 1980; 122:365-71.
12. Anderson SD, Seale JP, Rozea P, Bandler L, Theobald G, Lindsay BA. Inhaled and oral salbutamol in exercise-induced asthma. Am Rev Respir Dis 1976; 114:493-50.
13. Cockcroft DW, Killian DN, Mellon JJA, Hargreave FE. Protective effect of drugs on histamine-induced asthma. Thorax 1977; 32:429-37.
14. Williams SJ, Winner SJ, Clark TJH. Comparison of inhaled and intravenous terbutaline in acute severe asthma. Thorax 1981; 36:629-31.
15. Thiringer G, Svedmyr N. Comparison of infused and inhaled terbutaline in patients with asthma. Scand J Resp Dis 1976; 57: 17-24.
16. Dolovich MB, Killian D, Wolff RK, Obminski G, Newhouse MT. Pulmonary aerosol deposition in chronic bronchitics: IPPB versus quiet breasting. Am Rev Respir Dis 1977; 115:397-402.
17. Santolicandro A, Giuntini C. Patterns of deposition of labelled monodispersed aerosols in obstructive lung disease. J Nucl Med Allied Sci 1979; 23:115-27.
18. Dolovich MB, Ryan G, Hargreave FE, Newhouse MT. Aerosols: disposition and methods of administration. In: Middleton E Jr., Reed CE, Ellis EF, eds. Allergy: Principles and Practices. 2nd ed. St Louis: CV Mosby, 1983; 1:405-17.
19. Morrow PE. Aerosol characterization and deposition. Am Rev Respir Dis 1974; 110 (part 2):88-99.
20. Ruffin RE, Kenworthy MC, Newhouse MT. Response of asthmatic patients to fenoterol inhalation: a method of quantifying the airway bronchodilator dose. Clin Pharmacol Ther 1978; 23:338-45.
21. Lippmann M. Regional deposition of particles in the human respiratory tract. In: Lee DHK, Falk HL, Murphy SD, eds. Handbook of physiology, section IX – reactions to enviromental agents. Bethesda, Md: American Physiological Society 1977: 213-32.
22. Brain JD, Valberg PA. Deposition of aerosol in the respiratory tract. Am Rev Respir Dis 1979; 120:1325-73.
23. Newhouse MT, Ruffin RB. Deposition and fate of inhaled aerosols. Chest 1978; 73:936S-42S.
24. Pavia D, Thomson M, Shannon HS. Aerosol inhalation and depth of deposition in the human lung. The effect of airway obstruction and tidal volume inhaled. Arch Environ Hlth 1977; 32:131-7.
25. Dolovich MB, Sanchis J, Rossman C, Newhouse MT. Aerosol penetrance: a sensitive index of peripheral airways obstruction. J Appl Physiol 1976; 40:468-71.
26. Newman SP, Bateman JRM, Pavia D, Clarke SW. The importance of breathholding following the inhalation of pressurized aerosol bronchodilators. In: Baran D, ed. Recent advances in aerosol therapy. Brussels: UCB Pharmaceuticals, 1979:117-22.
27. Dolovich MB, Ryan G, Newhouse MT. Aerosol penetrance into the lung: influence on airway responses. Chest 1981; 80S:834-6.
28. Greening AP, Miniati M, Fazio F. Regional deposition of aerosols in health and in airways obstruction: a comparison with krypton-81m ventilation scanning. Bull Eur Physiopathol Resp 1980; 16:287-98.
29. Morgan MDL, Sing HBV, Frame MH, Williams SJ. Terbutaline aerosol given through pear spacer in acute severe asthma. Brit Med J 1982; 285:849-50.
30. Pederson JZ, Bundgard A. Comparative efficacy of different methods of nebulizing terbutaline. Eur J Clin Pharma 1983; 25:739-42.
31. Murray JF. A review of the state of the art in intermittent positive pressure breathing therapy. Am Rev Respir Dis 1974; 110 (Part 2):193-9.
32. Pierce AK, Saltzman HA, Chairman. Proceedings of the conference on the scientific basis of respiratory therapy. Am Rev Respir Dis 1974; 110 (Part 2):13-5.
33. IPPB Trial Group. Intermittent positive pressure breathing therapy of chronic obstructive pulmonary disease. Ann Intern Med 1983; 99:612-20.
34. Singer OP, Wilson WJ. Laryngotracheobronchitis: 2 years' experience with racemic epinephrine. Can Med Assoc J 1976; 115:132-4.
35. Eisenberg RS, Oatway WH. Nebulization of amphotericin B. Am Rev Resp Dis 1971; 103:289-92.
36. Shim CS, Williams MH Jr. Effect of bronchodilator administered by canister versus jet nebulizer. J Allergy Clin Immunol 1984; 73:387-90.
37. Corr D, Dolovich MB, McCormick D, Ruffin R, Obminski G, Newhouse M. Design and characteristics of a portable breath-activated particle size selective medical aerosol inhaler. J Aerosol Sci 1982; 13: 1-7.
38. Dolovich MB, Ruffin R, Corr D, Newhouse M. Clinical evaluation of a simple demand inhalation MDI aerosol delivery device. Chest 1983; 84:36-41.
39. Bloomfield P, Crompton GK, Winsey NJP. A tube spacer to improve inhalation of drugs from pressurized aerosols. Brit Med J 1979; 2:1479.
40. Berenberg MJ, Baigelman W, Cupples LA, Pearce L. Comparison of metered-dose-inhaler attached to an aerochamber with updraft nebulizer for the administration of metaproterenol in hospitalized patients. J Allergy Clin Immunol, accepted for publication.
41. Pierce AK, Sanford JP, Thomas GD, *et al.* Long term evaluation of decontamination of inhalation-therapy equipment and the occurence of necrotizing pneumonia. N Engl J Med 1970; 282:528-31.
42. Crompton GK. Problems patients have using pressurized aerosol inhalers. Eur J Respir Dis 1982; 63 (Suppl 119):101-4.
43. Epstein SW, Manning CPR, Ashley MJ, Corey PN. Survey of the clinical use of pressurized aerosol inhalers. Canad Med Assoc J 1979; 120:812-6.
44. Hodges IGC, Milner AD, Stokes GM. Assessment of a new device for delivering aerosol drugs to asthmatic children. Arch Dis Child 1981; 56:787-800.
45. Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johansson SA. Use of spacers to facilitate inhaled corticosteroid treatment of asthma. Am Rev Respir Dis 1984; 129:723-9.
46. Dolovich MB, Ruffin RE, Roberts RS, Newhouse MT. Optimal delivery of aerosols from metered dose inhalers. Chest

1981; 80S:911-5.
47. Newman SP, Pavia D, Clarke SW. How should a pressurized beta-adrenergic bronchodilator be inhaled? Europ J Respir Dis 1981; 62:3-21.
48. Thomas P, Williams T, Reilly PA, Bradley D. Modifying delivery techniques of fenoterol from a metered dose inhaler. Annals Allergy 1984; 52:279-81.
49. Heimer D, Chang S, Williams MH. The effect of sequential inhalations of metaproternol aerosol in asthma. J Allergy Clin Immunol 1980; 66:75-7.
50. Toogood JH, Baskerville JC, Jennings B, Lefcoe NM, Johansson SA. Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. J Allergy Clin Immunol 1982; 70:288-98.
51. Munch EP, Taudorf E, Weeke B. Dose frequency in the treatment of asthmatics with inhaled topical steroid. Eur J Resp Dis 1982; 63 (Suppl 122):143-53.
52. Latimer KM, O'Byrne PM, Morris MM, Roberts R, Hargreave FE. Bronchoconstriction stimulated by airway cooling. Am Rev Respir Dis 1983; 128:440-3.
53. Hughes JA, Tobin MJ, Bellamy D, Hutchison DCS. Effects of ipatropium bromide and fenoterol aerosols in pulmonary emphysema. Thorax 1982; 37:667-70.
54. Mygind N, Borum P. Effect of a cholinoseptor antagonist in the nose. Eur J Resp Dis 1983; 64 (Suppl 128):167-74.
55. Borum P, Olson L, Winther B, Mygind N. Ipratropium nasal spray: a new treatment for rhinorrhea in the common cold. Am Rev Respir Dis 1981; 123:418-20.
56. Dolovich J, Kennedy L, Kazim S, Vickerson F. Ipratropium bromide (Atrovent) nasal spray in vasomotor rhinitis. J Allergy Clin Immunol 1985; 75 (part 2):160.