Aerosol Therapy: Nebulizer vs Metered Dose Inhaler

The most common way of treating exacerbations of asthma and chronic airflow limitation (CAL) in hospital emergency rooms and on the wards is by means of bronchodilator aerosols generated by jet nebulizers. Thus, not surprisingly, physicians and their patients have come to believe that this method is the most efficacious form of aerosol therapy, and as a result, on leaving the hospital, these patients are often prescribed compressor-driven or ultrasonic nebulizers for domiciliary use.

This method of aerosol delivery has proliferated without solid scientific evidence demonstrating additional benefit compared with more convenient and less expensive aerosol generation using metered-dose inhalers. Previously, aerosol delivery by means of intermittent positive pressure breathing devices attached to nebulizers enjoyed unwarranted popularity for decades, only to be abandoned when convincing evidence became available that they were no better than nebulizers alone for administering bronchodilator aerosols. Published data, using standard dose regimens and suboptimal experimental design, suggested that there might be a therapeutic advantage to nebulizers vs MDIs.

In this issue (see page 804) Jenkins et al demonstrate convincingly that there is no advantage to bronchodilator therapy with nebulizers compared with effectively used metered-dose inhalers in patients with stable chronic airflow limitation. Their well designed, double-blind, double cross-over trial compared nebulized salbutamol and salbutamol from a metered-dose inhaler, using a cumulative dose-response technique to determine the optimum bronchodilator dose in the laboratory before initiating a domiciliary trial. In 9/19 patients, the MDI dose producing the greatest bronchodilatation was found to be greater than 200 μg. Thus, they established individualized, equivalent lung doses of drug with the two delivery systems while blinding patients and their physicians as to which delivery method contained the active drug. Interestingly, while all of their patients showed similar symptomatic improvement during the study no matter how the active drug was provided, all attributed their improvement to the nebulizer device. All but one wished to continue with the nebulizer at the end of the study despite the fact that there was no objective difference in response to the bronchodilator administered from either of the two delivery systems with respect to symptoms, peak expired flow rates or timed walking distance. Of particular interest is the fact that all four of their house-bound patients resumed walking outdoors—a result that may have been due to one or a combination of psychologic factors, improved compliance associated with training or the much larger than usual doses of the bronchodilator drugs administered by metered-dose inhaler in about 50 percent of the patients. The latter is a particularly important issue since there is good evidence that poor coordination, increasing airflow obstruction, a high inspiratory flow rate, low tidal volume, high respiratory frequency and severe airflow obstruction all conspire to reduce the aerosol dose delivered to the lower respiratory tract, thereby reducing the effectiveness of therapy, unless larger than usual doses of bronchodilator aerosols are used to achieve maximum bronchodilation.

If the data of Jenkins et al become widely accepted, there is the obvious potential for greatly reducing the cost of bronchodilator therapy while at the same time achieving the significant additional benefits of metered-dose inhalers, namely: ready portability, availability of virtually all therapeutic agents for treating reversible airflow obstruction (RAFO) and protection of the aerosol from the risk of bacterial contamination. During exacerbations of RAFO, 2.5-10 mg of nebulized adrenoceptor agonist solution has been recommended for effective therapy. However, until fairly recently, the recommended MDI-delivered dose under these conditions had not been specified, with the result that physicians tended to prescribe the recommended maintenance dose of two puffs of the bronchodilator of choice, which is usually suboptimal therapy under these circumstances. Little wonder then that patients (and physicians) have come to regard the nebulizer and bronchodilator solution as a more effective tool.

Several recent studies, and now including the one of Jenkins et al, have clearly demonstrated that the MDI is a more efficient and as effective an aerosol generator as the jet nebulizer and that optimum therapy is a matter of the dose of therapeutic agent delivered to the lower respiratory tract, both for maintenance therapy and during acute exacerbations, regardless of the
aerosol generation technique selected.8,9

In treating acute episodes of asthma in the emergency room, we have found it useful initially to provide four puffs of the adrenoceptor agonist bronchodilator of choice by MDI regardless of what the patient has apparently been taking recently (unless there is evidence of catecholamine overdose) followed by one puff each minute until subjective (and, if available, objective) benefit is achieved or side effects such as tremor, tachycardia or clinically important arrhythmia limit further drug administration. To assure aerosol delivery to patients unable to coordinate aerosol discharge and inhalation for home maintenance therapy (and invariably during acute exacerbations in the emergency room and for in-hospital therapy) we advocate a valved MDI add-on device such as the Aerochamber. Thus, the same aerosol delivery “system” can be used in-hospital or at home for acute exacerbations and for maintenance therapy, with adjustment of the dose of bronchodilator (or prophylactic “anti-inflammatory” aerosol) to the severity of the RAFO. We also teach the patient to appreciate that the need to use such large doses of bronchodilator acutely is an indication that their RAFO is out of control, requiring additional treatment, usually a short course of high dose systemic steroids, when these flare-ups occur.

Given the current “state of the art” of aerosol generation by MDI, the spectrum of drugs available in pressurized canisters and add-on delivery systems which assure aerosol delivery in infants, children and adults there is little reason to continue with the less efficient and more expensive means of administering drug solutions from nebulizers, except to those few patients in whom MDIs, even with appropriate add-ons, may be difficult to use.4

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References

Methylxanthines, Adenosine and the Pulmonary System

The purine nucleoside adenosine is a degradation product of adenosine triphosphate (ATP). Evidence suggests that adenosine has multiple physiologic actions.1 For example, because of its relaxation of vascular smooth muscle, it is implicated as a regulator of blood flow in a variety of organs, such as the heart, brain, skeletal muscles, and fat. In addition, adenosine is a presynaptic inhibitor and has been proposed to modulate neuronal activity.2 Alteration in adenosine metabolism, such as occurs in deficiencies of adenosine deaminase, results in disorders of the immune system.

Elsewhere in this issue of Chest (see page 874), Bowton and colleagues have documented the effects of aminophylline on cerebral blood flow in patients with chronic obstructive pulmonary disease. These investigators have documented a large decrease in cerebral blood flow after therapeutic dosages of aminophylline and they speculate that the alterations in brain function may well be related to these alterations in cerebral blood flow. Methylxanthines, such as aminophylline, have been documented to alter cerebral blood flow, but the mechanism of action is unclear. Methylxanthines inhibit cyclic AMP phosphodiesterase, mobilize calcium and release catecholamines.3 These effects are well known and occur at high concentrations of aminophylline. A less widely recognized action of methylxanthines is adenosine receptor blockade, which requires only low concentration of methylxanthine. The vast majority of the therapeutic and physiologic actions of methylxanthines probably occur because of adenosine receptor blockade. For example, the central stimulant actions of caffeine are attributed to the antagonism of the sedative effects of adenosine.4

Adenosine may also be involved in a variety of aspects of the pulmonary system. For example, it has been implicated in the central regulation of respiration, since adenosine and its analogs cause depression of respiration when applied directly into the central nervous system.5 Theophylline, long known to be a stimulant of the respiratory rate, appears to act by blocking the central actions of endogenous adenosine.6 Although lung adenosine concentrations appear to increase during acute pulmonary hypoxia,4 the data supporting the direct involvement of adenosine in pulmonary blood flow regulation is unclear.7 In normal patients, inhaled adenosine does not affect the bronchial tree, but in the asthmatic, adenosine causes bronchoconstriction, which is antagonized by theophylline.8 As Bowton and colleagues indicate, however, such therapy dramatically affects brain blood flow and alerts the clinician to important central nervous...