Aerosolized Drug Delivery in the 90s

Ten years ago the study of aerosol biology was confined to a few specialized laboratories and had limited relevance to the practice of medicine. In a 1994 Journal of Aerosol Medicine, I editorialized that aerosolized drug delivery was beginning to emerge as an applied science. Physicians and physiologists were reassessing aerosol delivery devices and wondering how best to target therapeutic agents to the lung. In 1996, the article by Hess et al herein (see page 498) represents the next phase of maturation for aerosols in medicine, that is, that new standards for applied research have been developed and should be used in defining drug delivery and that these standards should be known by practitioners in the field: pulmonologists and respiratory therapists.

Hess and colleagues emphasize the term “inhaled mass.” It represents the end point of drug delivery when using aerosols. That is, the mass of drug actually inhaled by the patient. It avoids many assumptions inherent in earlier techniques thought to predict drug delivery (eg, gravimetric changes in nebulizers, adjusting for solute concentration in the nebulizer fluid over time, temperature and hygroscopic effects, and tubing losses). Of equal importance, the inhaled mass technique includes the influence of the patient’s breathing pattern. Does the device function when used during tidal breathing? Panting? Pediatric breathing patterns?

How do we measure inhaled mass? An example is shown in Figure 1. A patient is receiving aerosolized pentamidine. The most important rule is to duplicate as closely as possible the actual clinical situation. By placing a filter at the mouthpiece, all particles presented to the patient are captured just before inhalation (left side of Fig 1). Those data are plotted over time in Figure 2. Drug activity as a percentage of the initial amount placed in the nebulizer is shown for a specific device, drug, and patient breathing pattern. Remarkably, the relationship is nearly straight until the nebulizer runs dry, that is, the amount of drug inhaled per minute does not vary in spite of changes in

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3 Marcy TW, Marinii JJ. Inverse ratio ventilation in ARDS: rationale and implementation. Chest 1991; 100:494-504
10 Huchon GJ. Radioaerosol studies of the pulmonary epithelium. In: Effros RM, Chang HK, eds. Fluid and solute transport in the airspaces of the lungs. New York: Marcel Dekker, 1994; 399-450
concentration and temperature in the nebulizer fluid. These curves can be obtained for most devices and breathing patterns on the bench by substituting a piston pump for the patient. Bench studies of inhaled mass are extremely useful in assessing devices, flow rates, baffles, and solution characteristics and hopefully will allow improvements in design of newer delivery systems.

Of course, knowledge of inhaled mass alone is insufficient in assessing the dose-response relationship to a drug. In basic studies of drug efficacy, deposition must be measured as well as the regional distribution of deposited particles (eg, pharynx, lung, etc). Those topics will not be addressed here. But no deposition study would be complete without a measure of inhaled mass because it allows differentiation between device and patient related factors in affecting deposition.3

What should the pulmonologist know about nebulizers and other aerosol devices? Ultimately, as much as they know about Swan-Ganz catheters and spirometry. While the average specialist may not measure inhaled mass, the principles of aerosol delivery should be known. In today’s hospital, important economic and clinical decisions require some knowledge of aerosol delivery. In your ICU are your ventilator/nebulizer combinations satisfactory for adequate drug delivery?4 Which devices should be used for mechanically ventilated vs spontaneously breathing patients?5

The study by Hess et al, while timely, emphasizes device performance with respect to bronchodilator delivery. Bronchodilators are important medications but their clinical effectiveness is relatively insensitive to issues related to drug delivery such as particle size distribution, deposition, and efficiency of nebulizers. They are administered clinically in the form of a “titration” with repeated doses given and response/toxicity determined at the bedside. In addition, bronchodilators are comparatively inexpensive and economic decisions regarding their use are more dependent on the therapist’s time and cost of materials. It is the newer, most costly drugs that will rely on thorough studies of aerosol delivery. The ultimate success of a clinical trial may depend on prior determination of inhaled mass. Is the drug actually nebulized? Is the delivery system efficient? Are the particles of reasonable size? What is the actual dose to the lung? On the hospital floor and in the office, the relatively simple considerations previously surrounding “giving a treatment” will no longer suffice for sophisticated drugs with complex effects. Those drugs, which were “on the horizon” in 1994—newer steroids, mucolytics, genes, antibiotics—are emerging now.

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REFERENCES
4 McPeck M, O’Riordan TG, Smaldone GC. Choice of mechanical ventilator: influence on nebulizer performance. Respir Care 1993; 38:897-95