
Respiratory Drug Delivery

“A vague idea of the benefit of inhalation in the treatment of diseases of the air passages is present in nearly all physicians; but it rarely assumes any tangible form, because of the dearth of information in the text books.”

John M. Scudder, MD, 1895

The science of aerosolized drug delivery has advanced greatly since the late 19th century, when the use of “medicated inhalations” was viewed by many as quackery (and much of it was). As information has accumulated, it has become clear that the delivery of aerosolized drugs to the lungs is a complex science, and that many variables influence the amount of drug that is deposited on the airway surface. Much of the impetus for research in this area stems from exciting new applications, such as the delivery of aerosol drugs for systemic use, or for the delivery of genetic material to treat diseases such as cystic fibrosis. In spite of a growing body of literature, too little attention is given to those variables affecting aerosolized drug delivery in both research studies and routine clinical use.

In this issue of CHEST (see page 1200), McPeek and colleagues compared drug delivery from a large-volume continuous nebulizer system with that from small-volume nebulizers. To simulate aerosol delivery to the patient, radiolabeled aerosol particles were nebulized and collected on filters at the mouth of a face model during ventilator-generated breathing. The amount of drug captured on the filter, measured as radioactivity, was defined as the “inhaled mass.” The study showed that the inhaled mass was similar for continuous nebulization and for intermittently filled small-volume nebulizers. The results are interesting in that they point out that only a fraction of the drug in a nebulizer is delivered to the patient, that there can be great variability in drug delivery among devices, and that breathing pattern can substantially affect the inhaled mass of a drug. While these are not new findings in aerosol science, they may not be common knowledge for those clinicians and respiratory-care practitioners who are administering inhaled drugs every day.

Bench measurements of nebulizer mass output and particle size characteristics can be helpful for quality control, but these measurements should not be used for predictions of lung dose or efficacy of a nebulized drug. The most accurate predictions of aerosolized drug delivery are those that use conditions most closely approximating the clinical setting, with a patient or patient surrogate breathing on a nebulizer. This can be done with a filter and ventilator set-up, as in the current study, or can be taken a step further, by quantitating lung deposition using gamma scintigraphy in subjects who have inhaled a radioactive aerosol. In experiments using a labeled aerosol, radioactive or otherwise, it is important to confirm that the label behaves similarly to the drug of interest.

The study by McPeek and coworkers points out the difference that breathing pattern can make in determining the inhaled mass of a drug, with implications that are especially pertinent in the pediatric population. For both the large-volume and small-volume nebulizer, the inhaled mass of the pediatric breathing pattern, compared with the adult breathing pattern, was reduced. Theoretical models of respiratory tract deposition have always indicated that breathing pattern will affect quantitative deposition, and experimental studies have corroborated this finding. Other factors that must be taken into consideration in predictions of respiratory drug delivery include the inherent interdevice variability of nebulizers of the same brand, particle size, and the possible changes in particle size and solute concentration that occur during nebulization. Although the variables may differ, similar considerations must also be made in examining drug delivery by metered-dose inhaler.

Even with close attention to all the variables and conditions mentioned previously, does an in vitro measurement accurately predict the in vivo lung deposition of drugs in a patient with lung disease? An additional layer of complexity is added when one considers the changes in lung architecture that can occur with disease. We know that the presence of obstructive lung disease alters the behavior of inhaled particles, affecting both the amount and location of deposition. Gamma camera lung scans in patients with asthma, COPD, and cystic fibrosis show increased particle deposition in the central airways and decreased particle penetration to the peripheral airways. These hot spots of increased...
central deposition are presumed to be at sites of airway obstruction. In general, the total amount of aerosol deposited in the lungs is usually increased in obstructive lung disease,\textsuperscript{13,14} and the lower the percent of predicted FEV\textsubscript{1}, the more central and heterogeneous the particle deposition.\textsuperscript{11} Much less information exists about aerosol deposition in other types of lung diseases (such as restrictive lung disease), or about inhaled particle deposition in children. Theoretical models indicate that younger children deposit a higher percentage of particles in airways than do adults.\textsuperscript{15} This would offset the reduction in inhaled mass noted for the pediatric breathing pattern in the current study.

Very few investigators have compared in vitro methods of estimating aerosol drug delivery with measurements of lung deposition in patients. In a study of subjects with HIV infection undergoing treatment with inhaled pentamidine, there was good correlation between inhaled mass as measured by filters and lung deposition measurements assessed by gamma scintigraphy.\textsuperscript{16} Pulmonary function testing in this group of patients showed primarily a restrictive defect with no evidence of obstructed airways. Similarly, studies using metered-dose inhalers and dry-powder inhalers showed good correlation between in vitro measurements using an anatomic throat model and in vivo measurements of lung deposition.\textsuperscript{17} Much of the human data in these comparisons, however, was collected from healthy volunteers.

So, the practice of aerosolized drug delivery has indeed progressed from quackery to science. In spite of these strides, much more attention must be given to consideration of variables, such as type of nebulizer, breathing pattern, and the severity and nature of the lung disease. This attention is needed not only in experimental and clinical studies, but also in clinical practice. It would be helpful to standardize techniques used for in vitro estimates of inhaled dose, using those methods that most closely approximate the clinical scenario. Studies that compare in vitro estimates of inhaled mass with lung deposition measurements in patients with lung disease are especially needed. Once again, I must defer to the wisdom of Dr. Scudder, who noted: “It is evident that much good might result from the judicious use of local applications to diseased surfaces, if these could be used with anything like the degree of definiteness that attaches their employment elsewhere.”\textsuperscript{1}

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\textbf{REFERENCES}


\textbf{Diagnostic Interpretation of Pericardial Fluids}

Pericardial fluid, normally measuring 15-35 mL, is mainly an ultrafiltrate of plasma, possibly with some overflow of myocardial interstitial fluid and lymph drainage.\textsuperscript{1} Protein concentration is lower in pericardial fluid.