Editorials

Aerosol Therapy: Assume Nothing and Require Data

In this issue of RESPIRATORY CARE, Mitchell et al[1] report a study in which they used a model of mechanical ventilation to examine differences in drug delivery between the hydrofluoroalkane (HFA) and chlorofluorocarbon (CFC) metered-dose inhaler (MDI) formulations of beclomethasone dipropionate (BDP). They discovered that the total emitted mass of drug at the end of the endotracheal tube (ETT) was greater with the HFA formulation, by a factor of 5.8. Aerosol particle size experiments showed that the particles exiting the end of the ETT were much smaller with the HFA-BDP formulation (mass median aerodynamic diameter of 1.2 μm, compared with 4.6 μm for the CFC-BDP) and that these smaller particles were more susceptible to hygroscopic growth under conditions of high humidity. The clinical implication of those findings is that in mechanically ventilated patients HFA-BDP may achieve greater lung delivery than CFC-BDP. Though delivery of inhaled steroids to mechanically ventilated patients in the intensive care unit is not as common as bronchodilator therapy (and not as well studied), there is increasing interest in using steroid aerosols in critically ill adults and infants with airway disease.[2,3]

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In a RESPIRATORY CARE editorial in the year 2000 Constantine Manthous wrote, "In aerosol treatments 'the devil is in the details'; practitioners should assume nothing and require data to demonstrate effectiveness for all devices and techniques used in the clinical arena."[4] I couldn't have said it better myself! The substitution of HFA for CFC propellant in MDIs, in response to the Montréal protocol for phasing out CFCs, is a good example of the importance of this principle. In the HFA-based formulation the BDP is in solution rather than in suspension (as in CFC formulations). The HFA formulation in combination with improved inhaler technology produces a smaller mean aerosol particle size than the CFC formulation,[5] and that particle size difference affects the location and quantity of drug deposition in the lungs and thus affects dosing, efficacy, and toxicity.

The report by Mitchell et al[1] presents a good opportunity to elaborate on important lessons for clinicians about aerosolized drug delivery.

1. *Physics is important.* Although I didn't think so at the time, everything I need to know I learned in Aerosol Physics 101. Respiratory therapists, physicians, nurses, and pharmacists receive very little instruction in the underlying principles governing the drugs and devices they use every day. Understanding how a particle's size affects its behavior in the lungs is one key to the successful treatment of airway disease with inhaled drugs. The mathematical prediction is that a larger proportion of HFA-BDP aerosol will penetrate to the smaller airways and less would deposit in the oropharynx, compared to CFC-BDP. Gamma camera scans of normal subjects who inhaled radiolabeled HFA-BDP confirmed that hypothesis.[6] Lung deposition of HFA-BDP was 53% of emitted dose, compared with 4% of the CFC-BDP aerosol. Pharmacokinetic studies also showed similar plasma levels of BDP when 400 μg of CFC-BDP was compared to 200 μg of HFA-BDP.[7] Clinical trials confirmed that, when compared with CFC-BDP, comparable asthma control could be obtained with approximately half the dose of HFA-BDP.[8]

2. *A change in drug formulation, device, or delivery conditions can affect dose delivered, efficacy, and/or toxicity*. This is the mantra of the aerosol scientist, and although you may have already gotten this message, it bears repeating. The particle size distribution and lung deposition of HFA-BDP had been well documented prior to the study by Mitchell et al.[1] There was no information, however, about the effect of an ETT or circuit humidification on the fine-particle aerosol produced by an HFA-BDP MDI. In fact, an in vitro study with a ventilator model and an HFA albuterol formulation showed less aerosol delivery with the HFA albuterol than with the CFC albuterol,[9] though it should be noted that the particle size distribution of the HFA albuterol is similar to that of the CFC product. Thus, it is important to test inhaled drug systems under the conditions they will be used, because the ventilator circuit and ETT impose additional variables into the drug delivery equation.

Prior investigations have confirmed that in the setting of mechanical ventilation, many factors—including location in the circuit, chamber use, timing, and humidification—can influence the dose delivered.[10] Most in vivo experiments have found lung deposition with a CFC-propelled MDI during mechanical ventilation to be in the range of 10–20% when conditions are optimized and the circuit is humidified. The ventilator model measurements by Mitch-

ell et al[1] would indicate that delivered drug mass of the HFA-BDP would be quite different than that expected from CFC-BDP, because of the smaller particle size. This sets the stage for confirmation by clinical trials with ventilated patients.

3. *Measurements using models are very helpful, but in vitro does not equal in vivo.* There is no substitute for measuring clinical outcomes of inhaled drug delivery; all theoretical predictions and in vitro measurements form the foundation for measurements in human subjects. In vitro measurements are important for quality control and comparison of devices, and can be used to estimate the amount of deposition in the respiratory tract. Though helpful for the design of in vivo measurements, in vitro estimates of drug delivery should never be extrapolated to predictions of clinical efficacy. In general, in vitro predictions have overestimated lung deposition amounts, compared with those measured in vivo by gamma scintigraphy or pharmacokinetic methods.[11] Mitchell et al[1] found an HFA-BDP-versus-CFC-BDP difference factor of 5.8:1 for total drug mass emitted at the end of the ETT, which is higher than expected and may not be borne out in clinical trials. High ratios were also found in a nonintubated model of the upper airway of an infant, in which the lung dose of HFA-BDP was 3.5–15-fold higher than CFC-BDP, depending on the tidal volume used.[12] In clinical trials, however, the comparative dose ratios of HFA-BDP versus CFC-BDP range from 1:1 to 2.6:1, based on clinical outcome measures.[13–15] One reason for the higher ratio in the Mitchell et al study[1] is that deposition was measured with a filter at the end of the ETT, which assumes 100% lung deposition of all particles exiting the tube; that would not be the case in vivo, where a portion of the inhaled particles would be exhaled. Because of the smaller particle size, it would be predicted that the deposited fraction of those particles entering the airways would be lower and the percentage exhaled would be higher than with the larger CFC-BDP particles.

4. *Clinical comparisons may differ greatly, depending on the dose used and the dose-response relationship of the drug.* When comparing drug delivery from different devices or with different formulations, it is important to give equipotent doses and to avoid doses on the plateau of the dose-response curve. Only studies that incorporate a dose-response comparison have the internal sensitivity to assure that errors are not being made when comparing different formulations. Studies of inhaled steroids require monitoring of clinical outcomes over a much longer period than studies of bronchodilators. Dose-response relationships are even more important for inhaled steroids, as greater pharmacologic potency does not always translate into greater clinical efficacy but can cause greater systemic toxicity.[16] In order to evaluate the relative potency of 2 inhaled steroid formulations, it is necessary to compare effects on the steep part of the dose-response curve. Failure to design studies with attention to dose-response relationships may explain discrepancies in clinical trials comparing the efficacy of HFA-BDP and CFC-BDP.

5. *The final lesson is that real life may supersede all preceding lessons.* All this attention to particle size, deposition amount, and dose-response relationships means nothing if the patient won't use the inhaler, doesn't use the inhaler correctly, or cannot afford to buy the inhaler. In vitro and in vivo studies and even clinical trials with human subjects are very far removed from real life and may only predict the optimal performance of inhaled drugs and devices. It is difficult to predict clinical efficacy and adherence with a given patient with any specific drug/device combination. So, in the end, there is no substitute for patient education. The best drug/device is the one the patient can and will use. Though in vitro and clinical testing of new formulations are key parts of inhaled drug development, we need to bring equal time and attention to the variables pertinent to the person wielding the inhaler.

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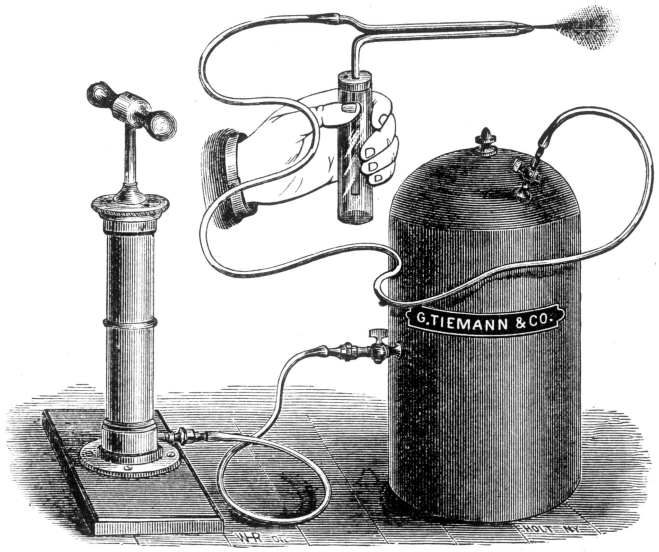

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