Liquid Nebulization: Emerging Technologies
Conference Summary

Dean R Hess PhD RRT FAARC

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Most physicians and respiratory therapists are knowledgeable of the use of aerosolized drugs, but many are less familiar with the performance characteristics of the nebulizer. In fact, the general opinion is that the performance of the nebulizer is relatively unimportant. However, there is accumulating evidence that the nebulizer itself does make a difference. The decision to replace a good performing nebulizer with a poor performing nebulizer may decrease the delivered dose in half or more. Although this is less important for routine bronchodilator therapy, it may make a big difference with newer aerosolized drugs. Increasingly, the Food and Drug Administration is approving drugs to be used with a specific nebulizer brand and new nebulizer designs are becoming available for use with these drugs. There are several reasons why I think this conference was important. First, new aerosol drug formulations are becoming available and these will require better performing nebulizers. Second, we as clinicians need to be knowledgeable of the newer generations of nebulizers so that we can make informed purchase decisions. Third, and perhaps most important, we must gain an increased appreciation for aerosol therapy as a science. The proceedings of this conference do much to synthesize the current state-of-the-art related to new nebulizer systems. This provides, in a complete and cogent manner, the scientific basis for which clinicians can improve their knowledge of the new generation of nebulizers. Key words: nebulization, aerosol, jet nebulizer, ultrasonic nebulizer. [Respir Care 2002;47(12):1471-1476]

Introduction

The nebulizer is one of the devices most commonly used by respiratory therapists (RTs). Drugs used in nebulizers have undergone intensive scientific scrutiny, including studies of indications, hazards, complications, and treatment schedules. Many physicians and RTs are fluent in the mode of action and recommended dose of nebulizer drugs, but most are relatively ignorant of nebulizer performance characteristics. Terms such as mass median aerodynamic diameter, dead volume, and inhaled mass are just not part of the lexicon of most clinicians. Nebulizer selection is usually based on price, and the nebulizer brand may be selected by the purchasing department rather than the respiratory care department. Unfortunately, the general sentiment is that it does not matter. Contrary to the evidence, the general thinking is that the drug can be placed in any nebulizer, enough flow is added to generate an aerosol, and the patient simply breathes the aerosol for 10 minutes.
The evidence is now clear that the nebulizer does make a difference. I published a paper more than 5 years ago that illustrated that there are considerable differences in output among commercially available nebulizers. The decision to replace a good performing nebulizer with a poor performing nebulizer may decrease the delivered dose by more than half. Perhaps this does not matter for routine bronchodilator therapy, but it can make a difference with drugs that are now becoming available. In the case of tobramycin, for example, it could mean the difference between effective therapy and ineffective therapy resulting in pseudomonas infection, or the difference between effective therapy and aminoglycoside toxicity. Increasingly, the Food and Drug Administration is approving drugs for use with specific nebulizer brands, and new nebulizer designs are becoming available for use with these drugs.

Why a Conference on Nebulizers?

Some might wonder why an entire conference devoted to nebulizers is important or necessary. In fact, some might point out that an entire conference on aerosol therapy was recently devoted to this topic. There are several reasons why I think this conference was important. New aerosol drug formulations and delivery devices are becoming available. In addition to the traditional agents to treat pulmonary airway and parenchymal disease, there is a burgeoning interest in aerosol medications with pulmonary vascular effects (vasodilators), systemic effects (insulin, narco-tics, and genetic effects (gene therapy). As Dr Geller pointed out in his presentation, there are 3 principal driving forces behind nebulizer innovations: (1) the ban on chlorofluorocarbon propellants commonly used in metered-dose inhalers, (2) the inefficiency of existing nebulizer designs, which is particularly an issue with new formulations, and (3) the increasing interest in using the inhalation route to deliver drugs to the circulation.

As clinicians we need to be knowledgeable about the new generation of nebulizers so that we can make informed purchase decisions. Perhaps most important, we must gain an increased appreciation for aerosol therapy as a science. As is the case in other aspects of medicine, our practice of aerosol therapy should be evidence-based. As discussed throughout this conference, there is convincing evidence that the choice of nebulizer does make a difference, particularly for newer devices and formulations. I have often wondered why it is that, while we want evidence to support many of the therapies we use, we consider nebulizers as gadgets. We need to get away from the "bronchodilator mentality" in which the choice of nebulizer is generally considered unimportant. We need to remember that the formulation is worthless when combined with an ineffective delivery device. Perhaps this explains the failed aerosol surfactant trial for acute respiratory distress syndrome. We need to think of the nebulizer and the formulation together as a unit, similar to the way we see metered-dose inhalers and dry powder inhalers, in which the drug and device are packaged as a single unit. As defined by Dr Dennis during his presentation, the nebulizer is a device (sold separately from the drug solution) that converts the liquid to aerosol droplets. The nebulizer system, on the other hand, includes the nebulizer, the formulation, the gas that powers the nebulizer, and the patient interface.

As clinicians we are responsible for instructing patients in the correct use of nebulizers, so we must understand how to use them effectively. As pointed out by Dr Rubin in his presentation, for nebulizer therapy to be effective the nebulizer must work well, the nebulizer-patient interface must work well, and the patient must "work well," meaning that the patient must know and use proper technique. The challenge is then to build an outstanding nebulizer that the patient will use correctly.

The presenters in this conference included many of the world's authorities on nebulizers and aerosol therapy. As seen in these conference proceedings, nebulizer designs are becoming increasingly sophisticated. To paraphrase a comment made by Dr Smaldone during the conference, we need not only smart nebulizers but also clinicians who are informed in the appropriate use of these devices. For me this conference has made many nebulizer issues less nebulous and has demystified many concepts (please excuse the puns). It is my pleasure to summarize this conference.

Background

Dr Rau kicked off the conference with a thorough discussion of the design principles of traditional jet and ultrasonic nebulizers currently in widespread clinical use. He pointed out that many factors are known to affect jet nebulizer performance, and he distinguished between 3 jet nebulizer types: constant output, breath-enhanced, and breath-actuated (dosimetric). He also described the performance of ultrasonic nebulizers, which use a piezoelectric effect to produce aerosol.

Several important issues were discussed after Dr Rau's presentation. One was repeated nebulizer use and the resulting performance degradation. Jet nebulizers are typically designed as single-patient-use devices, but with domiciliary use the nebulizer may be cleaned and reused hundreds of times. Another issue related to domiciliary use is compressor performance. Some compressors may generate inadequate flows, and even the best performing nebulizer may perform suboptimally when used with a poorly performing compressor.

In his presentation Dr Rau presented a list of desirable characteristics for a nebulizer for clinical use. From the ensuing discussion and the subsequent presentations I gen-
Table 1. Performance Characteristics of an Ideal Nebulizer

<table>
<thead>
<tr>
<th>Performance</th>
<th>Characteristics</th>
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<tbody>
<tr>
<td>Reliable performance</td>
<td>independent of fill volume, flow, power, and</td>
</tr>
<tr>
<td></td>
<td>ventilatory pattern</td>
</tr>
<tr>
<td>Appropriate particle size</td>
<td>Simple to use for caregiver and patient</td>
</tr>
<tr>
<td>Performance independent of formulation and carrier gas</td>
<td>Operation independent of position</td>
</tr>
<tr>
<td>Efficient dose delivery</td>
<td>Portable</td>
</tr>
<tr>
<td>Multiple dose delivery</td>
<td>Easy to clean, difficult to contaminate</td>
</tr>
<tr>
<td>Minimal environmental contamination</td>
<td>Durable</td>
</tr>
<tr>
<td>Quiet, patient-friendly</td>
<td>Cost-effective</td>
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Dr. MacIntyre addressed the special situation of delivering an aerosol through an endotracheal tube (ETT). As he showed, the pathway through an artificial airway is narrower than that of the native airway. However, it is well known that aerosol can be delivered through an ETT. It is generally believed that aerosol delivery through an ETT is inferior to delivery through the native upper airway, but, as Dr. MacIntyre pointed out, there are few if any comparison data. Moreover, differences can be minimized by careful attention to the details of aerosol administration.

As also pointed out by Dr. MacIntyre, much variability (5-40%) of dose delivery through ETTs has been reported. This is related to the many factors known to affect the delivered dose, including ventilatory pattern and timing, characteristics of the carrier gas (humidity and density), nebulizer performance characteristics, particle size, ventilator and circuit properties, and ETT size (particularly for neonates). The issue of aerosol delivery to neonates, which was raised during the discussion after Dr. MacIntyre's presentation, is a special problem because of the small size of the ETT, the rapid, shallow breathing pattern, the use of ventilators with bias flow, and the use of high-frequency ventilators.

Dr. MacIntyre also described a catheter device that is passed through the ETT and generates aerosol at the distal tip of the ETT, thus bypassing all of the issues related to delivering the aerosol through the ETT. The role of that device is yet to be determined. Whether it will be most useful for delivery of agents such as bronchodilators or agents such as surfactants remains to be determined.

Dr. Rubin addressed issues related to the use of nebulizers in children and provided several important tips for clinical use of nebulizers in that age group. The dose of drug placed into the nebulizer should not be adjusted for the age of the child. He also pointed out that nebulizer therapy works best if the patient is breathing quietly (there is about 75% greater aerosol delivery if the child is breathing quietly). Dr. Rubin also pleaded with clinicians to abandon the practice of blow-by aerosol therapy for infants, as this is completely ineffective.

Dr. Rubin pointed out that there are a number of factors that affect patient and family compliance with nebulizer therapy, including the cost of the therapy, poor patient and family education (in which RTs can play a key role), adverse effects of the medications (e.g., taste), and the time requirements for the therapy. He also indicated that a poor patient response to nebulizer therapy may be the result of prescribing the wrong drug or making the wrong diagnosis.

Professor Dolovich addressed methods to assess nebulizer performance. As she indicated, there are a number of reasons to conduct in vitro testing of nebulizers. These include testing of variability in manufacturing between units, assessing temperature changes during nebulization, assessing drug output with simulated or actual breathing patterns, and particle size characteristics of the aerosol generated. Ideally this testing should be conducted under the usual conditions of use. For complete assessment, clinical response data are necessary.

A variety of techniques have been used to assess nebulizer performance, including standing cloud measurements and unit dose collection. Particle size can be determined using a cascade impactor, laser diffraction technique, or liquid impinger. Measures of drug output from nebulizers include assessing the drug content in the aerosol, assessing the drug content remaining in the nebulizer after the delivered dose, and gravimetric techniques. If a breathing pattern is used to assess aerosol delivery from a nebulizer, this may be a simulated breathing pattern or an actual breathing pattern and may simulate a normal breathing pattern or a disease breathing pattern.

As discussed after Professor Dolovich’s presentation, the principal advantage of in vitro assessments of nebulizer performance is in comparing devices. In general, in vitro models underestimate in vivo aerosol delivery to the lung. Appreciating the limitations of in vitro assessments of nebulizer performance, these are likely to continue to be important. This is particularly important as new nebulizer designs become available and their performance relative to existing devices needs to be established.

Dr. O’ Riordan discussed the issue of drug formulations and their effects on nebulizer performance. The formulations placed into nebulizers may be solutions, suspensions, or nanosuspensions. Characteristics of the formulation can affect nebulizer performance, even for bronchodilators. Interestingly, nebulizers that perform poorly with solutions might perform better with suspensions. Characteristics of the formulation that might affect nebulizer perfor-
Fig. 1. Value is the relationship between quality and cost. High value occurs when quality is high and cost is low.

mance include volatility, isotonicity, and viscosity. The formulation can also affect patient tolerance, such as with alcohol versus propylene glycol solvents.

As indicated by Dr O’Riordan, there is increasing interest in delivering aerosolized liposomes into the lung, to increase nebulizer output of medications, potentially increase the residence time in the airway, and as vectors for aerosolized gene therapy. In the case of liposomes the nebulizer may affect the formulation. For example, liposomes may be affected by shear stress in a traditional jet nebulizer or heat in an ultrasonic nebulizer. As new nebulizer formulations become available, the nebulizer/formulation interaction will probably become increasingly important.

Mr Dunne addressed issues related to the cost-effectiveness of nebulizer therapy. He suggested that the principles of pharmacoeconomics can be applied to nebulizer therapy. He then described some economic analysis and its application to nebulizers, including cost-effectiveness, cost/benefit, and cost/utility. Mr Dunne suggested that there are several barriers to the clinical acceptance of a new generation of nebulizers that have a higher unit cost than currently used devices. First, traditional nebulizers are inexpensive and their limitations are accepted by clinicians. Second is the issue of caregiver indifference—the so-called “bronchodilator mentality” mentioned above.

Acceptance of a new generation of nebulizers, which are likely to have a higher unit cost than presently available devices, will challenge the provincial myopia. That is, we will need to look at the overall value of the nebulizer. Value is the relationship between quality and cost (Fig. 1). High-value nebulizers will be those that greatly increase the quality of patient care for a small increase in cost. Furthermore, cost includes more than just the price of the device. It also includes issues such as the cost of training caregivers in the use of the device, teaching patients how to use the device correctly, and the impact of the device on other important issues affecting cost, such as hospital days.

After Mr Dunne’s presentation an interesting discussion ensued about caregiver protection during nebulizer ther-apy. This issue has generated some interest since the recognition of a higher risk of asthma among RTs, which was speculated to be due to repeated exposure to bronchodilator aerosol.14 This concern has been more or less dismissed by RTs. There has been concern related to aerosolized pentamidine and ribavirin, and caregiver protection is recommended when those agents are administered. This concern has resurfaced with the increasing use of other aerosolized drugs, such as antibiotics. Of concern is that repeated low-level exposure to these agents could contribute to future drug resistance. There is also concern regarding the potential for exposure to other drugs under development, but the extent of that risk is not fully known. However, it seems prudent to consider caregiver exposure when nebulizers are developed for new drug formulations.

Unfortunately, Dr Robert Meyer from the Food and Drug Administration was not able to attend the conference. In his absence, the attendees discussed regulatory issues related to nebulizers. Traditionally, nebulizers and the drug formulations used in nebulizers were developed by separate manufacturers. That is quite different than the development of metered-dose inhalers and dry powder inhalers, in which the drug and delivery system is considered a drug-device combination. Increasingly, however, new drugs for inhalation are assessed as drug-device combinations. A recent example is that of nebulized tobramycin, in which the drug was approved for use with a PARI nebulizer. In the future, it is likely that new drugs for inhalation and the nebulizers used with those drugs will be assessed as drug/device combinations. This creates potential practical issues. Imagine, for example, that a drug/nebulizer combination is approved, but the drug and the nebulizer are provided by different manufacturers. What happens if the nebulizer is discontinued? Depending on the clinical importance of the drug, this could potentially have catastrophic results.

New-Generation Nebulizer Designs

Dr Geller, Dhand, Gomez, and Smaldone described the designs and performance of the new generation of nebulizers, which was a particularly difficult assignment because there is very little in the peer-reviewed literature describing these devices and much of what is known is proprietary. Because these devices are in various stages of development, the amount of information available in the public domain is limited. These reports presented more detailed information on these devices than is available anywhere else in the literature.

Dr Geller described systems, such as Respimat and AERx, that create aerosols by forcing pressurized liquids through orifices. Dr Dhand described systems, such as those by Aerogen and Omron, that use vibration to force liquids through multiple orifices. Dr Gomez described sys-
tems that use electric fields to produce aerosols. Dr Smaldone described "smart" nebulizer designs, including the AeroEclipse, Halolite, and AKITA. There are a number of characteristics that these devices have in common, as shown in Table 2.

In his presentation Dr Smaldone discussed the importance of matching the performance of the nebulizer to the physiology of the patient. Although this should go without saying, it occurs to me that this is not often considered when choosing a nebulizer. As clinicians we match ventilator settings to the physiology of the patient, and we match oxygen delivery devices to the physiology of the patient, so of course we should match the nebulizer to the physiology of the patient.

Standardization and the Future

Dr Dennis discussed issues related to standardization of testing methods for nebulizers. Although such standards do not currently exist in the United States, they have been developed in Europe. The British standards were published in 1994, and the European standards were published in 2001. By and large these are type-testing standards and do not involve clinical testing. There are also European Respiratory Society nebulizer guidelines, which are evidence-based and match nebulizer output data to the drug and the patient.

As the final presentation of the conference, Dr Barry discussed the future of nebulization. He identified 3 issues that need to be addressed when developing future generations of nebulizers. We need to find ways to improve patient compliance, and unfortunately little is known today about how to do that. New formulations will be developed and we will need the appropriate nebulizers. We need to develop better nebulizers that are smaller and more portable, that provide value-added features, and that allow more precise and reproducible drug delivery. Increasingly we need to consider the nebulizer and the drug as a unit. In fact, therapy may be ineffective if a great inhalable drug is coupled with a poorly performing nebulizer.

<table>
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<tr>
<th>Role to be defined: bronchodilators or new formulations?</th>
<th>Yes</th>
<th>No</th>
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<tr>
<td>Efficient: large dose in small time; much larger dose than traditional nebulizer</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Minimal dead volume</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Independent of compressor; self-powered</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Small and portable</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Can nebulize a wide variety of formulations; some are formulation-specific</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Breath-actuated</td>
<td>Yes</td>
<td>No</td>
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Table 2: Common Characteristics of the New Generation of Nebulizers

Fig. 2. Three criteria should be assessed when a new device is considered. We should adopt new technologies that are technically feasible, clinically useful, and cost-effective.

A Few Final Thoughts

I will complete my summary by referring to a concept introduced by Dr David Pierson when he summarized a RESPIRATORY CARE Journal Conference many years ago. New nebulizers will certainly be developed. As clinicians, we need to consider 3 issues related to these new devices. First, is the concept technically possible? Second, is the concept clinically useful? And, finally, is the concept cost-effective? We should adopt the use of equipment that is technically feasible, clinically useful, and cost-effective (Fig. 2).

REFERENCES


