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SPECIAL ISSUE

LIQUID NEBULIZATION: EMERGING TECHNOLOGIES PART II

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CONFERENCE PROCEEDINGS

- Nebulizers That Force Pressurized Liquids Through Nozzles
- Nebulizers That Use a Vibrating Mesh or Plate with Multiple Apertures
- The Electrospray and Its Application to Targeted Drug Inhalation
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Standardization Issues: In Vitro Assessment of Nebulizer Performance

John H Dennis PhD MSc

The delivery of nebulized drugs is poorly controlled and the choice of the most appropriate delivery device is poorly understood, particularly because of off-license prescriptions and a lack of evidence-based medicine. Standardized in vitro methods for measuring nebulizer performance have been adopted in Europe, by the 2001 publication of a European Standard, prEN13544–1. These standardized methods were subsequently incorporated within the European Respiratory Society nebulizer guidelines, which will provide clinicians with useful information to improve nebulizer therapies. Standards for measuring nebulizer performance should be considered in North America and elsewhere. Careful consideration should be given to either adopting the methods embodied in the European Standard or developing the basis for developing that standard further through the International Standards Organization. Either way, confusion among clinicians would be reduced and nebulizer safety and aerosol delivery efficiency increased by standardizing in vitro methods of nebulizer performance assessment. *Key words: nebulizer, nebulization, aerosol, standard, standardization, testing, Europe, International Standards Organization, ISO, Comité Européen de Normalisation, CEN, in vitro assessment.* [Respir Care 2002;47(12):1445–1455]

Introduction

Although delivering nebulized drugs to the lungs has been used for centuries in medical research, and nebulizers and nebulizer drugs have been commercially available throughout the past century,[1] the delivery of nebulized drugs is still poorly controlled and poorly understood by the clinical community.

Prescription drugs delivered orally, intravenously, and via aerosol inhalation from metered-dose inhalers and dry powder inhalers undergo clinical trials to prove the drug's safety and efficacy. This is not the case with the many drugs used for nebulization, which are prescribed off-license and bypass regulatory requirements. Nebulizers are regarded as cheap and convenient plastic devices that readily generate an aerosol (Fig. 1) that will contain whatever drug solutions or suspensions are placed in them for delivery to the respiratory tract. Rarely is the nebulizer delivery device specified on the prescription. Rather, only

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Fig. 1. A typical jet nebulizer, showing release of aerosol.

the drug solution volume and concentration are specified. This leaves open the choice of nebulizer by which to deliver the off-license drug aerosol. The decision of what device to use is often left up to the local doctor or nurse, and sometimes even a hospital clerk, to choose whatever device is either conveniently to hand or has become the hospital's standard nebulizer for that period. The nebulizer is often chosen with little or no objective justification other than the manufacturer's performance claims or, more often, simply the lower cost of a particular nebulizer. The reader should recognize that there is a wide range of performance among nebulizers. If, say, 2 mL of a given drug solution was placed into all available nebulizers, the dose delivered could vary greatly.[2] The lack of regulation and understanding in matching the prescribed drug with the nebulizer implies that the quality, consistency, and control of the delivered dose are poor.

There are 2 main types of nebulizer, jet (or pneumatic) and ultrasonic, which have different operating characteristics (recently reviewed by Hess[3]) and can be described in terms of their overall performance as either constant-output, breath-enhanced, or dosimetric.[2] Each nebulizer brand has specific characteristics that determine its aerosol output, including total rate of aerosol output, rate of aerosol delivered to the patient, dead volume (solution remaining in the nebulizer after nebulization has ceased), and particle size characteristics. Some nebulizers are most efficient at delivering small droplets to the peripheral lung, some nebulizers are better suited to deliver larger particles in the upper airways, and, in my opinion, some nebulizers are not suited to drug aerosol delivery at all. But how is the clinician to know which nebulizer to use for which patient? What criteria can the clinician use to make an informed decision?

Many methods have been described to measure the "performance" of particular nebulizer designs.[4,5] For instance, measurement of aerosol output using weight loss has been undertaken for decades and is still commonly used. However, weight loss measures both aerosol output and evaporated solvent, and evaporated solvent typically accounts for half of the weight loss over a nebulization period. In some particularly inefficient nebulizers, evaporation can account for more than 75% of the weight loss.[6] Alternatively, total aerosol output can be estimated by measuring the amount of drug solution left in the nebulizer cup. This method can provide a measure of the total drug aerosol emitted and is not confounded by evaporative losses, but it does not reflect the aerosol delivered to the patient, as most nebulizers commonly allow inhalation of only 40–70% of the emitted dose. There is a similar problem with methods that collect all emitted aerosol on a filter, followed by subsequent analysis of the filtered residue. Though all these methods produce data, the results cannot reflect the in vivo situation. This, in my opinion, makes them weak methods on which to base a nebulizer standard, as the results are divorced from the clinical setting.

Measuring aerosol particle size is equally confusing. Cascade impactors, which are commonly used to measure aerosol particle size from metered-dose inhalers and dry powder inhalers, can drastically distort the aerosol size by causing full evaporation of the nebulized aerosol. Laser diffraction (scattered light) size measurement of aerosol droplets cannot take into account droplet evaporation, which is inherent in all constant-output aerosol designs. For both aerosol output and aerosol droplet size many different results are possible from the same nebulizer, depending on the measurement method used.

The relative merits of the various methods to assess in vitro nebulizer performance have been debated in the literature for decades, often by individuals or small groups with greater or lesser amounts of training in aerosol and clinical sciences. From all the different views one common message emerges, namely that the method used should reflect the amount and droplet size of aerosol received by the patient.[7] In other words, the in vitro test should reflect the in vivo dose delivered. However, though that is a commonly held objective, over the past 50 years researchers have not naturally regressed to a commonly accepted nebulizer test method. And because nebulized drugs have escaped regulatory control, no national or international body had been commissioned to examine the science and produce standard methods. Or at least that was the situation

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until the early 1990s, when the United Kingdom's standards body made the first attempt at standardizing test methods, by publishing a British Standard.[8,9] Though the British Standard methods had limitations (Table 1) the existence of the published standard became a focal point for debate and progress. In the late 1990s the issue of standardizing in vitro methods to assess nebulizer performance was tackled more comprehensively by the European Standards Organization (Comité Européen de Normalisation or CEN), culminating in the research and development of new nebulizer in vitro test methods published as a European Standard.[10]

The present review summarizes standardization issues inherent in the in vitro measurement of nebulizer performance, describes the scientific and clinical principles underlying the European Standard, introduces the principles underlying the clinical nebulizer guidelines recently published by the European Respiratory Society, and describes how the European Respiratory Society adopted the standard testing methods of the European Standard.

Standardization Issues

There may be a perception that "standardization" could be interpreted as making things the same: making them a standard size, shape, color, or, in the case of nebulizers, similar in terms of performance, as measured by aerosol output and aerosol droplet size. That is not the intended meaning of *standardization* in this review.

There are many types, designs, and brands of nebulizer, with a great range of aerosol output and droplet size. I regard this as a good thing, because different drug solutions and suspensions are targeted to different parts of the airways, in different doses. Therefore different nebulizer designs are needed for different patients and settings (pediatric versus adult, intensive care versus home care), with different delivered aerosol doses and different droplet sizes required for different patients and therapies. Thus a wide range of nebulizer designs and performances are needed, ideally with each nebulizer medication being matched to a particular window of nebulizer performance. However, difficulty arises when clinicians are faced with numerous devices and manufacturer claims of performance characteristics. How should a clinician make the choice of what nebulizer system is best suited to a particular patient or patient group for effective delivery of a particular medicine?

In choosing the ideal nebulizer to deliver a particular drug, the clinician should take into account the intended site of aerosol deposition (upper and/or lower respiratory tract), which largely determines the required aerosol droplet size, depending on the patient's age and disease state, desired dose, treatment time, and patient compliance with the treatment. In addition, cost constraints can limit the choice of nebulizer. At present a major difficulty is that information on nebulizer performance is not presented to the clinician in any meaningful way.

Information on nebulizer output and aerosol droplet size can be entirely absent or only loosely described in marketing jargon (eg, "best performing nebulizer," "clinically proven," "preferred by over 90% of users") without any scientific justification of the claims. Of course not all nebulizer manufacturers are so vague in describing the performance of their devices. Many manufacturers actively promote, or at least have available, technical literature on their devices. However, those performance data can be obtained with a wide variety of laboratory methods. However well-informed the clinician, performance data are very dependent on the method by which they were obtained—so

Table 1. Strengths and Weaknesses of British Standard 7711, Part 3, Specification for Gas-powered Nebulizers for the Delivery of Drugs

Strengths	*Comment*
First formal national standard relating to jet nebulizers	Focused attention on assessment of nebulizer performance and provided a platform for debate and technical research and development.
Adopted a chemical tracer rather than weight loss to evaluate nebulizer performance	Standard practice relied on weight loss, which grossly overestimated true aerosol output because of concurrent evaporation to compressed and ambient air.
Weaknesses	
No use of breathing pattern in assessing inhaled aerosol	This is particularly important for assessing the performance of breath-enhanced and dosimetric nebulizer designs.
Does not extend to ultrasonic nebulizers	Modern designs of ultrasonic nebulizers (eg, Omron nebulizer) have solved many past technical limitations and are expected to become more common as their advantages are recognized in the health care market.
Relies on laser diffraction to estimate particle size	Laser sizing takes no account of solute concentrating effects, particularly in the smaller particles, and provides a volume/size distribution invariably larger than the solute size (dry particles) distribution, which is of far greater clinical relevance and interest.
Applies laser diffraction to size a "standing cloud"	Nebulizer aerosols rapidly evaporate in ambient air, such as the air entrained over constant-output nebulizers or through breath-enhanced nebulizers.

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much so that the data may be meaningless, as with aerosol output measured by weight loss or solute loss, with or without breathing simulation. Yet that is usually the only type of information the clinician is expected to use in deciding about off-license nebulization of a drug. It is difficult if not impossible for the average clinician, who is not an expert in nebulizer design and function, to make an informed decision on which device is best for which patient. For that reason the focus in this review is to persuade the reader that some amount of standardization of in vitro aerosol measurement methods is desirable. Such standardization would provide a commonly derived data set for all nebulizer designs, which would (1) be more easily interpreted than the type of data currently available, (2) help clinicians determine the most appropriate nebulizers for particular patients and patient groups, and (3) improve patient safety and aerosol delivery efficiency.

At the risk of laboring the point for the need for standardizing nebulizer performance testing, consider the following analogy with the automobile industry. Cars come in a range of shapes and sizes and are intended for different purposes. Most car buyers know what basic design they require, but choosing the exact brand and model can be difficult. Like nebulizers, the manufacturer's marketing information is invariably biased toward its own product. Though this may make interesting reading for the enthusiast, it should not be relied upon for an objective decision. We can rely on reviews by experts who offer their opinions on subtle differences between models, but those views are individual and invariably biased by previous prejudices and current affiliations. Consider the information available for estimating fuel economy. If this important performance criterion were left solely up to the manufactures to provide, they would no doubt as an industrial group regress to making the measurement starting from the top of a mountain with a tailwind in order to bias the fuel economy figure as far as possible. That does not happen because standardized test methods for fuel economy have been developed to gain more realistic and comparable data. We must rely on objective information supplied by standardized methods to make an objective and fully informed decision. For example, data on trunk (called "boot" in the United Kingdom) space, acceleration, servicing costs, and depreciation are independently obtained. The methods for obtaining these data are refined to be as realistic and repeatable as practicable. Data that prove unrealistic are of little use. Methods that cannot be repeated are of little value. What is true for the automotive industry and marketplace is largely true for the nebulizer industry and marketplace.

To date there has been little, if any, standardization in the nebulizer industry and marketplace. I believe the industry would welcome standardization, as would most clinicians and nebulizer users. Standardization of in vitro performance measures would improve patient safety and aerosol delivery efficiency, and, in the long term, standardization can help provide a more solid foundation for development of better nebulizer technologies, because manufacturers will know that the marketplace is better prepared to recognize and appreciate the real benefits of new technologies. At present if a manufacturer produced a better nebulizer, how would the clinician know? It would just be absorbed into the marketplace as yet another "best performance" nebulizer claim, with perhaps a few supporting papers written by individuals with personal bias and affiliation. It is for these reasons that some standardization is required.

European Nebulizer Standard

The European Standard developed over a period of 6 years, involving all European national standards bodies (eg, United Kingdom's British Standards Institution, Netherlands Organization for Applied Scientific Research) working within CEN, the European umbrella organization. Most scientists and clinicians with a serious interest in nebulizer testing and clinical application were involved, either directly or indirectly. For the first time, a critical mass of clinical and scientific experts were brought together to focus on how best to standardize the measurement of nebulizer performance. Though the European Standard on nebulizers addresses a number of regulatory issues, most are beyond the scope of the present review. What is important here is that the European Standard facilitated the development of in vitro testing methodologies that were thoroughly discussed and evaluated prior to acceptance by the European clinical and scientific aerosol community. Aspects of the European Standard have been described elsewhere.[11] Some of the more important principles are introduced and summarized below.

Nebulizer Versus Nebulizer System

The European Standard recognizes that different nebulizers will deliver different doses of drug to the same patient, even if all conditions such as breathing pattern and nebulizer fill volume are controlled. This is because some nebulizers are inherently more efficient than others. For example, consider the most common nebulizer design, the constant-output nebulizer, which probably accounts for more than 70% of the nebulizers in home and hospital use today. A constant-output nebulizer emits aerosol at a constant rate until the volume of drug solution in the nebulizer cup is so small that nebulization ceases. The rate of aerosol output is constant, regardless of whether the patient is inhaling, breath-holding, or exhaling. This implies that for at least half the duration of operation the nebulizer is emitting aerosol into the ambient air. Not only is this extremely

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