A Comparison of Pulmonary Availability Between Ventolin (Albuterol) Nebules and Ventolin (Albuterol) Respirator Solution*

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The two most common albuterol preparations used for nebulization are: (1) Ventolin (albuterol) respirator solution (Glaxo Canada Inc; Montreal, Canada) of which 2.5 mg (0.5 mL) is diluted with 2 mL of normal saline solution, and (2) the preservative-free, prediluted Ventolin (albuterol) Nebules PF (Glaxo) (2.5 mg/2.5 mL). The two preparations were compared using both a Hudson 1720 “T” up-draft Neb-U-Mist jet nebulizer and a Hudson 1730 “T” up-draft Neb-U-Mist II jet nebulizer (Hudson; Temecula, Calif), which were driven by a compressor (Pulmo-Aide; Devilbiss; Somerset, Pa) and by dry compressed air at 6 and 8 L/min. Particle size distribution was measured with a particle sizer (Malvern 2600; Malvern Instruments; Malvern, UK) and drug output for the nebulizer was calculated from the differences in predrug and postdrug volume and concentration. Drug availability was defined as the amount of drug carried in particles less than 5 μm in diameter. Drug availability was greater with the albuterol respirator solution, due to the surface activity of the preservative benzalkonium chloride, for both nebulizers but particularly for the 1720. Differences in drug availability between nebulizers exceeded fourfold depending on the preparation, the nebulizer, and the nebulizing flow. These differences could not have been predicted from the manufacturer’s specifications. The results suggest that prediction of drug availability must be based on measurements with the specific preparation and the specific nebulizer used.

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Key words: aerosol; albuterol; bronchodilator; nebulization

Abbreviations: MMD=mass median diameter; NEB=nebule; PA=Pulmo-Aide; RF=respirable fraction; Vd=dead volume; VRS=Ventolin respirator solution

A frequently used method of albuterol administration, in both the hospital and the home environment, has been via wet nebulization. This has been particularly true in the pediatric population. Generally, a solution constituting 0.5 mL (2.5 mg) of albuterol (Ventolin Respirator Solution [VRS]; Glaxo Canada Inc; Montreal, Canada) and 2 mL of normal saline solution is nebulized with a commercially available jet nebulizer. In the hospital, the nebulizer is normally driven by a dry-compressed gas source, either air or oxygen, whereas in the home environment the most common means is with a compressor. Nebulization is usually continued until there is no visible output from the nebulizer. Recently, one manufacturer (Glaxo Canada Inc) developed a nebul (Ventolin nebule PF [NEB]), containing a preservative-free, prediluted (2.5 mg) albuterol solution that has very quickly become popular for its ease of use. The predilution reduces the risk of dosage error and is much more convenient and quick to use. Based on the information supplied by the manufacturer, the only difference that exists between the two albuterol preparations is the addition of the preservative benzalkonium chloride to the VRS. In addition to benzalkonium chloride having been known to provoke bronchoconstriction in some patients, it also appears to change the physical-chemical properties of the albuterol solution. Simply, if one was to shake equal amounts of both albuterol preparations, VRS and NEB, the VRS would form bubbles that have a greater stability than those formed from the NEB.

The process of nebulization produces an aerosol...
that has a distribution of spherical particles over a range of sizes. Although the larger particles contain more drug than the smaller ones, it is only those particles less than 5 \( \mu m \) in diameter that are likely to enter and deposit in the lungs. Those particles larger than 5 \( \mu m \) in diameter tend to deposit in the posterior pharynx due to inertial impaction.\(^2\) Hence, it is that volume of aerosol in particles less than 5 \( \mu m \) that constitutes the respirable fraction (RF).\(^3\) Since the particle size distribution depends on the physical-chemical properties of the solution being nebulized, as well as the characteristics of the nebulizer and the driving flow of the nebulizer, we compared two albuterol preparations using two standard commercially available jet nebulizers to determine whether the different formulations of albuterol influenced the amount of aerosolized drug that is likely to deposit in the lungs.

**Materials and Methods**

The two jet nebulizers compared were the Hudson 1720 *T* up-draft Neb-U-Mist and the Hudson 1730 *T* up-draft Neb-U-Mist II (Hudson; Temecula, Calif.). These nebulizers have been used extensively in our institution. Both nebulizer model types were the traditional nonvented jet nebulizers with a T connector and mouthpiece mounted to the exit port. The Hudson 1720, the larger of the two, has an estimated internal surface area of 86 cm\(^2\) and is designed with a removable baffle. The smaller 1730 has an estimated internal surface area of 67 cm\(^2\) and is designed with a permanent, nonremovable baffle. The internal surface area was estimated from the geometric shape of all parts, including the baffles. The information supplied by the manufacturer suggested a satisfactory mass median diameter (MMD) for the nebulizing flows of 5, 6, and 8 L/min for both nebulizers. For the Hudson 1720, the stated MMD was 7.0, 6.5, and 5.5 \( \mu m \), respectively, and for the 1730, it was 7.5, 6.6, and 6.3 \( \mu m \), respectively. No details of the methods were supplied with the manufacturer’s information.

Measurements were made in triplicate using three individual nebulizers of each model type (one measurement for each nebulizer) to assess particle size distributions and nebulizer drug output. For each of the three individual nebulizers, particle size distributions were initially determined using a volume fill of 3 mL normal saline solution and a driving flow of 8 L/min to determine reproducibility between nebulizers of the same model type.

The nebulizers were driven by either a commercially available compressor (the Pulmo-Aide [PA] compressor; Devilbiss; Somerset, Pa.), used for ambulatory care by our institution and others,\(^a\) or by a dry compressed air source via a flowmeter that was specifically calibrated to deliver flows of 6 and 8 L/min to each nebulizer. The PA produced a flow of 6.0 L/min when driving the 1720, and 5.3 L/min when driving the 1730. The flowmeter for the dry compressed air source was manufactured to be “back pressure compensated” so that it would not be affected by the resistance of the nebulizer. This compensation, however, was only partial and a specific calibration curve was constructed for each nebulizer by measuring volume over time of the gas leaving the nebulizer.

The nebulizers were weighed on an electronic balance empty, before and after (Mettler PM6000; Fisher Scientific; Ottawa, Canada). Following each run, the nebulizers were washed and dried with a high-pressure air source, with original dry weight confirmed for each nebulizer. The nebulizing solution consisted of either 0.5 mL (2.5 mg) VRS mixed with 2 mL of normal saline solution or the NEB (2.5 mg albuterol precluded with normal saline solution to 2.5 mL). Nebulization was allowed to continue until there was no visible mist for a period of at least 10 s, which was defined as end nebulization.\(^9\) The residual volume at end nebulization will, for clarity, be referred to as the dead volume (Vd). It was assumed that any concentrating of the drug during nebulization would be due to evaporative losses\(^7\) and would be reflected both in osmolarity changes of the nebulization solution and by UV spectrophotometry. Prior to the study, the nebulizers were run for selected times to allow varying degrees of concentration of the nebulizing solution. Samples were taken both before and after nebulization to determine osmolarity changes, measured by freezing point depression (Multi-Osmette 2430; Precision Instruments Inc.) and UV absorbance at a wavelength of 228 nm using a spectrophotometer (Hewlett Packard 8453; Montreal, Canada). When a Bland and Altman\(^1\) analysis indicated that both methods gave virtually identical results with no bias, the simpler method of using changes in osmolarity was adopted for the study. The postnebulization drug concentration was calculated based on the change in osmolarity. Total drug output was based on the prenebulization and postnebulization weights and predrug and postdrug concentrations, derived from the following formula:

\[
\text{Total drug output} = \frac{\text{drug} - \text{concentration} \times \text{preosm} \times \text{Vd}}{\text{postosm}} \quad (\text{mg})
\]

The nebulizers were clamped vertically and the output of the mouthpiece was directed across the helium-neon laser beam of a particle sizer (Malvern 2600 Series; Malvern Instruments; Malvern, UK). Particles entering into the helium-neon beam of the Malvern 2600 will scatter light. This scattered light passed through a 63-mm lens (Fourier optics) and onto a detector composed of concentric rings placed at the focal length of the lens. Smaller particles scatter light to a greater extent than larger ones so that the smaller the particle size distribution, the greater the energy reaching the outer rings of the detector.\(^14\) From the distribution of the energy received, the particle size distribution of the aerosol can be calculated. The mouthpiece was placed 4 cm from the 63-mm receiving lens.\(^14\) Measurements were made throughout the nebulization period with each measurement requiring 2,000 individual detector sweeps. The particle size distribution was calculated using a model independent fit and the presentation “particles in air.” In choosing “particles in air,” the anomalous theory, which is appropriate for partial transmission of light through the particles, was utilized. The particle size distributions are based on volume diameter measured in micrometers. Since the aerosol droplets from the nebulizers are spherical, one can assume that the volume diameter is equivalent to the aerodynamic diameter. From the distribution of particle sizes, the RF was calculated as the fraction of the volume of aerosol contained in particles of less than 5 \( \mu m \) diameter. Particle size distributions were determined with three jet nebulizers of each model type (1720 and 1730) for each nebulizing solution (VRS and NEB) and for each of the three flows (PA, 6 L/min, 8 L/min). Particle size distributions were performed throughout each individual run until the point of intermittent aerosol output. Initial particle size distributions (first 90 s) were discarded because it has been suggested that the nebulizers required some time to reach steady-state conditions.\(^16\) After this initial period, repetitive measurements were virtually identical. From the triplicate measurements for each condition, the MMD and the RF were determined. The drug availability was considered to be the drug output times the RF.
Table 1—Total Drug Output, RF, and Vd*

<table>
<thead>
<tr>
<th>Flow</th>
<th>PA 6 L/min</th>
<th>8 L/min</th>
<th>PA 6 L/min</th>
<th>8 L/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRS, mg</td>
<td>0.64</td>
<td>0.59</td>
<td>0.65</td>
<td>1.44</td>
</tr>
<tr>
<td></td>
<td>(0.60, 0.68)</td>
<td>(0.48, 0.69)</td>
<td>(0.54, 0.77)</td>
<td>(1.41, 1.47)</td>
</tr>
<tr>
<td>NEB, mg</td>
<td>0.38</td>
<td>0.35</td>
<td>0.41</td>
<td>1.37</td>
</tr>
<tr>
<td></td>
<td>(0.25, 0.51)</td>
<td>(0.32, 0.38)</td>
<td>(0.34, 0.49)</td>
<td>(1.35, 1.39)</td>
</tr>
<tr>
<td>RF</td>
<td>0.38</td>
<td>0.36</td>
<td>0.52</td>
<td>0.41</td>
</tr>
<tr>
<td></td>
<td>(0.35, 0.41)</td>
<td>(0.33, 0.39)</td>
<td>(0.47, 0.57)</td>
<td>(0.39, 0.43)</td>
</tr>
<tr>
<td>VRS-Vd, mL</td>
<td>1.66</td>
<td>1.58</td>
<td>1.36</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>(1.48, 1.83)</td>
<td>(1.38, 1.78)</td>
<td>(1.08, 1.64)</td>
<td>(0.58, 0.93)</td>
</tr>
<tr>
<td>NEB-Vd, mL</td>
<td>2.00</td>
<td>1.92</td>
<td>1.81</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>(1.81, 2.18)</td>
<td>(1.83, 2.00)</td>
<td>(1.70, 1.91)</td>
<td>(0.89, 1.0)</td>
</tr>
</tbody>
</table>

*Values are means and 95% confidence limits; n=3 for all conditions.

Because of the observation of greater bubble stability of the VRS, surface tension measurements of both nebulizing solutions and a 0.01% w/v solution of benzalkonium chloride were performed 4 times each using the Wilhelmy plate technique at 25°C. This was done to determine whether the addition of the preservative to the VRS changed the surface activity of the solution.

RESULTS

The results showed that the total drug output of both nebulizers was greater with the VRS as compared with the NEB (p<0.0005 for the 1720 and p<0.005 for the 1730, paired t test) with a smaller Vd remaining for the VRS (p<0.0005 for both nebulizers [Table 1]). Visual observation during nebulization demonstrated large drops continually forming on the walls of both the nebulizers when NEB was the agent and foam when VRS was the agent. At the end of nebulization, the large droplets of the NEB solution adhered to the walls of the nebulizer, thereby increasing the Vd. This was most marked with the larger walls of the 1720 (Table 1). With the VRS, the foam continuously ran back into the reservoir at the base of the nebulizer allowing more of the solution to be nebulized, thereby giving rise to a smaller Vd.

Particle size distributions between the two preparations when compared for the same nebulizer differed only slightly, although one of the 1730 nebulizers consistently gave a particle size distribution that was slightly but consistently larger than the other two. It can be seen that the higher the nebulizing flow the smaller the MMD (Table 2) and the greater the RF (Table 1). There were no significant differences, however, in total drug output at the different flow rates for each nebulizer type (Table 1).

For the 1730, nebulization times for the PA, 6 L/min, and 8 L/min were 6 min, 6 min, and 3 min for the VRS and 4 min, 4 min, and 2 min for the NEB. For the 1720, nebulization times were 9 min, 8 min, and 5 min for the VRS and 8 min, 7 min, and 4 min for the NEB.

Drug availability, which was the total drug output times the RF, was always greater for the VRS than the NEB, with the exception of the 1730 using the PA, where there is overlap of the 95% confidence limits of the means. These differences between solutions were more striking with the 1720 than the 1730, although overall, there would be more drug available to a patient when using the 1730. These results are summarized in Table 2.

Surface tension measurements of the two solutions yielded results of 35.0±0.5 mN/m for the VRS and

Table 2—Drug Availability and MMD*

<table>
<thead>
<tr>
<th>Flow</th>
<th>Hudson 1720</th>
<th>Hudson 1730</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PA 6 L/min</td>
<td>8 L/min</td>
</tr>
<tr>
<td>VRS, mg</td>
<td>0.24</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>(0.23, 0.25)</td>
<td>(0.19, 0.23)</td>
</tr>
<tr>
<td>NEB, mg</td>
<td>0.14</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>(0.12, 0.16)</td>
<td>(0.12, 0.14)</td>
</tr>
<tr>
<td>MMD, μm</td>
<td>6.12 ± .30</td>
<td>6.30 ± .30</td>
</tr>
</tbody>
</table>

*Values are means and 95% confidence limits; n=3 for all conditions.
70.5±0.3 mN/m for the NEB, which is very close to that of water. The surface tension of a solution of 0.01% w/v benzalkonium chloride was measured in triplicate and was found to be 27.3±0.4 mN/m.

**Discussion**

The results of this study demonstrate that patient drug availability depends on the particular preparation used as well as the nebulizer type and the flow used to drive the nebulizer. For the 1720, drug availability was 60 to 70% greater for the VRS compared with the NEB. While the 1730 is clearly a superior nebulizer, this could not have been predicted from the information supplied by the manufacturer. Furthermore, few if any centers prescribing drugs by wet nebulization make a major distinction between the flows used to drive the nebulizers despite both the manufacturer-supplied information and the aerosol literature\(^\text{5,18}\) that attests to a smaller particle size distribution when using higher driving flows. In terms of particle size distribution, both nebulizers performed better than the claims made by the manufacturer.

The major difference between the two albuterol preparations is the lower surface tension of the VRS compared with the NEB. Both by observation of the large droplets adhering to the walls of the nebulizer with the NEB compared to the foam of the VRS and the lower Vd values seen with the VRS, it is clear that the surface activity of the VRS formulation enhanced drug output. The larger internal surface area with increased area for droplet adherence seen with the 1720 is likely to be an explanation as to why the differences between the two preparations were greater with this nebulizer compared to the 1730. What is more difficult to explain is the slight and not statistically significant decrease in albuterol output by the 1730 driven by a nebulizing flow of 8 L/min compared to 6 L/min for both nebulizer solutions. This is accompanied by a corresponding increase in Vd. This may be a chance finding or, alternatively, the high flow in the smaller 1730 may have kept drops of the solution up on the walls of the nebulizer by aerodynamic forces alone and hence prevented them from running back into the reservoir where they would undergo renebulization.

This study emphasizes the principle that any alteration in the physical-chemical characteristics of a nebulizing solution may have unexpected results in the amount of drug that would be available to patients. There is no suggestion in any of the literature supplied by the manufacturer (Glaxo) that the dose to the patient would be altered by the presence or absence of the surface active preservative. Furthermore, many physicians are not aware of the magnitude of the differences in aerosols produced by different nebulizers using different driving flows. What is unclear are the clinical implications of these results. Because of the high reproducibility of these in vitro studies, findings that may be statistically significant may not be clinically significant. This is almost certainly true when comparing the outputs of the 1730 at equivalent flows between the two nebulizing solutions. However, the output of the 1720 driven by the PA is almost doubled by the use of the VRS compared to the NEB. Looking across nebulizers and flows, the lowest drug availability was 0.14 mg for the NEB in the 1720 driven by the PA compared to 0.84 mg for the VRS in the 1730 driven at 8 L/min (Table 2). In this case, it would be expected that there would be clinical differences, either in the form of improved response or increased side effects or both. The data in Table 2 are presented as the mean drug availability in milligrams and 95% confidence intervals of the mean to enable the individual clinician to decide the preparation and route that he or she would prefer. The decision on what is likely to be or not to be a clinically significant difference is clearly related to a number of factors, which include the patient’s condition and the goals of therapy. Furthermore, it is important to realize that drug availability differs from drug inhalation, the latter being dependent on the phase (ie, inspiration) and pattern of breathing.\(^\text{19}\)

In conclusion, this study shows that two preparations of albuterol, each containing 2.5 mg of drug in a total of 2.5 mL, could result in a clinically significant difference in the drug available to the patient depending on the choice of preparation, nebulizer, and flow. Such differences could result in either underdosing, overdosing, or inconsistencies in therapeutic response. The only way to avoid problems of this nature is to test the output of each nebulizer under the expected conditions of use and to adjust the dose accordingly.

**References**

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