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Exposure of home-attending healthcare workers to aerosolized medications (simulation study)

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ABSTRACT

Home-attending healthcare workers (HHCWs), one of the most rapidly growing occupations worldwide, are exposed to a wide range of aerosol contaminants, including pharmaceuticals administered to patients in their homes by nebulizer treatment. The aerosol concentration and exposure patterns may be vastly different from those identified in hospital environments. Inhalation exposure of healthcare professionals to nebulized medications has not been quantified. This pilot simulation study was conducted to measure particles released from a commercially available nebulizer-based aerosol delivery system into the indoor environment. Aerosolized medications such as Ipratropium Bromide, Budesonide, and Albuterol Sulfate (all suspended in a NaCl solution), and NaCl (used as medication to treat respiratory symptoms) were evaluated in individual trials. Deionized water was used as a control. The aerosols were measured using an Electrical Low Pressure Impactor at three locations of the HHCW-simulating manikin relative to the aerosol source. Exposure to all four selected aerosolized medications was significant (exceeding background control by one to four orders of magnitude). The particle size distributions measured for the four aerosols at a fixed distance from the source demonstrated similar trends with no significant differences identified in most cases. Although the total aerosol mass concentration in the breathing zone of the simulated HHCW ranged widely, from 2.29 to 10.2 $\mu g/m^3$, it was not significantly affected by medication type. Therefore, we concluded that NaCl can serve as a surrogate for assessing aerosol exposures, at least for the selected nebulizer-administered medications.

1. Introduction

The use of nebulizers, a drug delivery device used to provide medication in the form of a mist inhaled into the patient's lungs, is widespread in both inpatient and outpatient settings. When healthcare workers administer medications by nebulizer, they may be exposed to these medications and are put at health risks that are greater than if they administer medications orally or intravenously (Croteau et al., 2004). Studies have demonstrated that respiratory therapists have an increased risk for asthma (Christiani & Kern,

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1993; Dimich-Ward, Wymer, & Chan-Yeung, 2004; Kern & Frumkin, 1989). Exposure of healthcare workers to pentamidine isethionate aerosolized by a nebulizer has been documented (Beach, Campbell, & Andrews, 1999; O'Riordan & Smaldone, 1992). As inhalation therapy performed by a nebulizer on a daily basis is often the best option for treating asthma, cystic fibrosis, and chronic obstructive pulmonary disease (Ibrahim, Verma, & Garcia-Contreras, 2015), it is widely used in home healthcare. Since exposure to aerosols may impact the potential for asthma and other health effects, such exposures warrant additional characterization.

Home-attending healthcare workers (HHCWs), one of the most rapidly growing occupations across the globe, are exposed to a wide range of aerosol contaminants, including pharmaceuticals administered to patients in their homes via nebulizer from a NaCl-based liquid suspension. There are two common types of nebulizers used in the home environment. While they differ in the mechanisms used for the aerosol generation from a liquid suspension, the particle size near the source ranges from 1 to 5 μm depending on the model and the manufacturer (Ibrahim et al., 2015). Jet nebulizers are more frequently utilized because they are relatively inexpensive and easy to use (Gardenhire, Ari, Hess, & Myers, 2013). Droplets in exhaled breath can be transmitted over short and long distances between a patient and a worker (Papineni & Rosenthal, 1997). For instance, Hui et al. (2009) reported that healthcare workers can be exposed to exhaled air of a patient receiving nebulizer treatment within 79 cm.

The aerosol concentration as well as exposure patterns of aerosols nebulized in a home environment are often unique and may significantly differ from those identified in hospital settings. This is due to differences in relative humidity, air exchange rate, efficiency of air filtration/purification, room size and other factors. It is particularly important that HHCWs operate in an uncontrolled environment of patients' homes where the only option for them to reduce the risk of exposure is to use personal protective equipment (PPE). At the same time, it has been reported that as many as 33% of respiratory therapists do not use PPE during nebulizer treatment (Dimich-Ward et al., 2004). Furthermore, approximately 88% of respondents administering antibiotics with a nebulizer did not always use eye/face protection or respirators because of lack of awareness of the hazards or due to the assumption that exposures are inconsequential (Tsai, Boiano, Steege, & Sweeney, 2015). Many HHCWs enter the patients' homes unprotected or wearing surgical masks, which provide rather low protection against aerosol particles in these settings (Elmashae, Grinshpun, Reponen, Yermakov, & Riddle, 2017).

To summarize, inhalation exposure of HHCWs to aerosolized medications during nebulizer treatment remains insufficiently evaluated. Therefore, there is a need for an investigation, which would assess inhalation exposure to NaCl-based medications aerosolized with a jet nebulizer by measuring the particle number concentration and size distribution in the breathing zone of an HHCW. A laboratory simulation using manikins was conducted as an initial approach for determining if this exposure is significant. Additionally, we hypothesized that NaCl can serve as a surrogate for selected nebulizer-administered medications in future field studies.

2. Materials and methods

2.1. Generation of aerosolized medications and aerosol measurement

The experimental set-up designed and built for this pilot laboratory simulation study is shown in Figs. 1 and 2. The tests were

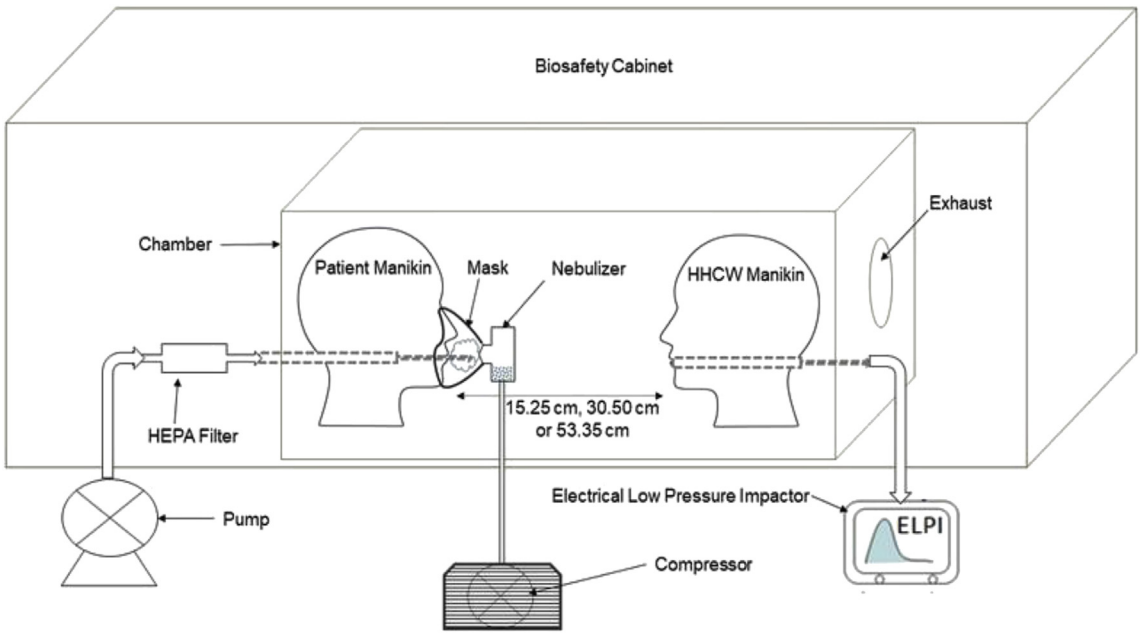

Fig. 1. Experimental setup inside a Class II Biosafety Cabinet.

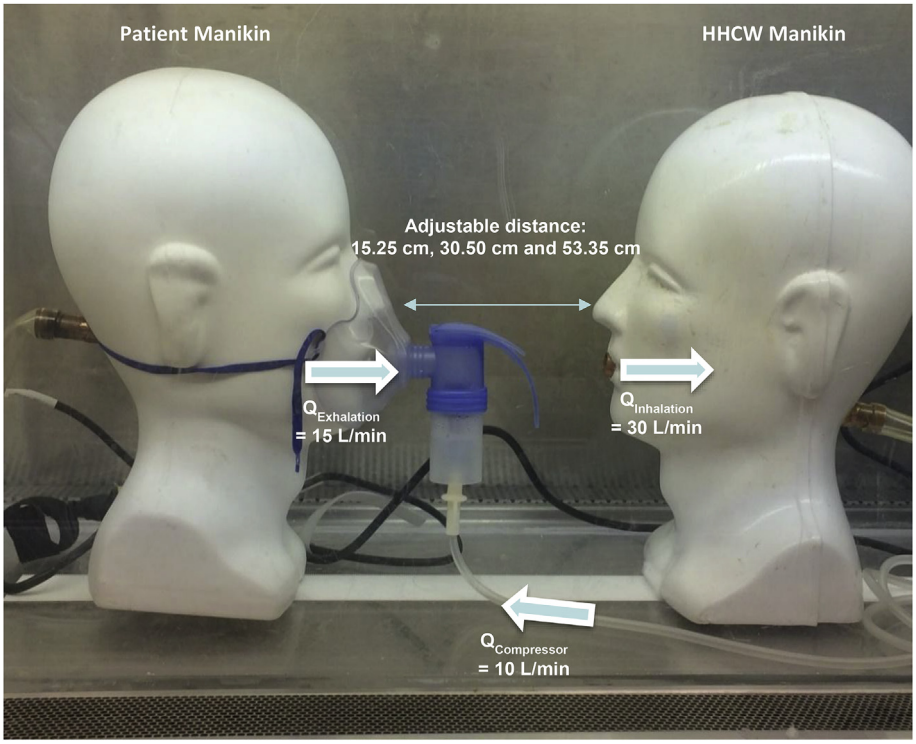

Fig. 2. Photo: two manikins inside the chamber.

conducted in a rectangular simulation chamber (dimensions ≈ 112 cm × 30 cm × 43 cm) with an opening on one side behind the HHCW-simulating manikin. The chamber was placed inside a Class II Biosafety Cabinet (SterilchemGARD; Baker Company, Sanford, ME, USA) to avoid exposure of the study's investigators to the tested medications. The tested aerosolized medications were generated, one at a time, by operating a commonly used Vios PRO Compressor with the reusable LC Sprint nebulizer and the PARI's PRO-Vent Adult Mask (PARI Respiratory Equipment Inc., Midlothian, VA, USA) operating at 10 L/min. This aerosol delivery system is approved for use by the FDA Center for Devices and Radiological Health (CDRH). The system was designed for heavy use and is commonly used in the home healthcare setting. The same aerosol delivery system was utilized for the control aerosol generated from deionized water. The mask and nebulizer apparatus was attached to the mouth of the patient-simulating manikins. A pump connected to this manikin operated at a constant push air flow at a rate of 15 L/min. The latter simulated an exhalation-only flow regime. This was established as a "worst-case scenario" as compared to a conventional inhalation-exhalation cycle aiming at maximizing the aerosol output. The other manikin simulating a HHCW was placed at different distances from the aerosol source. An adjustable valve was used to control HEPA-filtered air flow and humidity inside the chamber.

An Electric Low Pressure Impactor (ELPI, Dekati, Kangasala, Finland), was used to measure in real time the particle concentration and size distribution of the aerosol in the breathing zone of the HHCW-simulating manikin. A prior pilot study utilizing the capabilities of the ELPI as a cascade enabled us to verify that the particle size distribution at the mouth of the manikin was fairly represented by the data recorded by this instrument (i.e., the wall losses in the sampling lines and other factors that could affect the sample representativeness were not significant). The ELPI measures eleven particle size ranges between 29 nm and almost 10 µm. With a real-time measurement capability, it produces a particle size distribution every 5 s. The 5-second readings are integrated over the sampling time to yield the particle size distribution recorded in the database.

The ELPI sampled through the mouth of this manikin at an air flow rate of 30 L/min. The latter represents a typical peak inspiratory flow for a healthcare professional treating a patient. Each experiment was performed for 5 min so that each data point for a specific particle size was calculated as a geometric mean (GM) of 60 ELPI readings. With three distances, five substances (four medications and control) tested in three replicates, 11 particle sizes and 60 readings per test, our database included $3 \times 5 \times 3 \times 11 \times 60 = 29{,}700$ ELPI readings.

2.2. Selection of tested aerosolized medications

To select the aerosolized medications for our study, a home healthcare provider in the Cincinnati area was consulted to identify a list of aerosolized medications most commonly used for a nebulizer treatment in patients' homes. Additionally, we found that, according to Dimich-Ward et al. (2004), the most frequently used aerosolized medications are Albuterol (81%) and Ipratropium bromide (62.0%) – both from NaCl solutions. Saline (NaCl) itself is widely used as medication, e.g., for treating some respiratory

symptoms. As a result, the following medications were selected to be tested in this study:

1) Ipratropium Bromide Inhalation Solution 0.02%, 0.5 mg per 2.5 mL (Nephron Pharmaceuticals Corporation, West Columbia, SC, USA),
2) Budesonide Inhalation Suspension 0.5 mg per 2 mL (Sandoz Inc., Princeton, NJ, USA),
3) Albuterol Sulfate Inhalation Solution 0.083%, 2.5 mg per 3 mL (Nephron Pharmaceuticals Corporation, West Columbia, SC, USA),
4) NaCl (APP Pharmaceuticals, Inc., Schaumburg, IL, USA).

The first three medications (Ipratropium Bromide, Budesonide, and Albuterol) were used premixed and suspended in a solution of NaCl. All above-listed medications are approved by the U.S. Food and Drug Administration (FDA) and the Center for Drug Evaluation and Research (CDER) for use with the nebulizer. In addition, deionized water (Water Saver Faucet, Co., Chicago, IL, USA) was selected as a control.

2.3. Selection of distances between the patient- and an HHCW-simulating manikins

Three distances, 6 inches (15.25 cm), 12 inches (30.50 cm) and 21 inch (53.35 cm), between the aerosol source (mouth of the patient-simulating manikin) and the receptor (mouth of the HHCW-simulating manikin) were chosen for testing as reasonable estimates to represent different scenarios of an HHCW handling the nebulizer treatment. The first (15.25 cm) corresponds to checking/adjusting the nebulizer during treatment (close proximity). The second (30.50 cm) represents the situations when the healthcare worker holds the device with his/her elbow angled at 90°. The third distance (53.35 cm) is an estimate made for the device being held with a stretched arm (180°) or when the healthcare worker stands next to the patient.

2.4. Calculation of the total mass concentration

The particle size distributions of the four test and one control aerosolized substances obtained by the ELPI were used to calculate the particle mass distributions and, subsequently, the total aerosol mass concentrations. The molecular weights for these compounds are the following: Ipratropium bromide = 430.4 g/mol ($C_{20}H_{30}BrNO_3H_2O$), budesonide = 430.5 g/mol ($C_{25}H_{34}O_6$), and Albuterol sulfate = 576.7 g/mol ($C_{26}H_{44}N_2O_{10}S$). To determine the densities of particles generated from the three drugs suspended in NaCl solution, we performed a separate experiment. At a fixed distance, the aerosol particles were collected with the ELPI impactor and each stage was gravimetrically analyzed for determining the mass increase that occurred during aerosol sampling. By knowing the aerosol concentration, flow rate, and sampling time, we calculated the number of particles of a specific size fraction collected on each stage and, subsequently, the density of these particles. The measurement conducted at 6 inches from the source showed that for the particles from 0.044 to 2.04 μm, which accounted for > 90% of all particles by mass, the density varied from 1.700 g/cm^3 (the largest size) to 2.165 g/cm^3 (the smallest size). This suggests that the particles initially generated by the nebulizer as droplets evaporated rapidly losing most of their liquid content while traveling the first 6 inches from the source. The nominal density of NaCl, 2.165 g/cm^3, was used across the board as the particle density in the calculations to conservatively estimate the aerosol mass concentration (its upper limit).

The total aerosol mass concentration C_m was calculated as follows

$$C_m = \frac{\pi\rho}{6}\int_{d_{p.min}}^{d_{p.max}} d_p^3 C(d_p) d(d_p) \tag{1}$$

where ρ is the particle density, d_p is the particle diameter specified for each ELPI size channel, $d_{p,min}$ and $d_{p,max}$ are lower and upper boundaries of the particle size range selected for testing in this study, and $C(d_p)$ is the number concentration of particles of diameter d_p.

The particle mass median aerodynamic diameter (MMAD) was determined from the count median diameter (CMAD) as follows (Hinds, 1999; Kulkarni, , Baron, & Willeke, 2011):

$$MMAD = CMAD \exp(3\, Ln^2\sigma_g) \tag{2}$$

where σ_g is the geometric standard deviation.

2.5. Data analysis

The data analysis was performed using R, v.3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). The data sets were log-transformed before analysis.

A one-way analysis of variance (ANOVA) followed by pairwise comparisons conducted with the Tukey honestly significant difference test (Zar, 2010) was deployed to study the effects of a distance between the source and receptor and the differences in the particle size distribution, the calculated particle fractional mass distribution, and the calculated total aerosol mass concentrations for different suspensions. For all the comparisons examined in this study, a p-value of < 0.05 represented a significant difference.

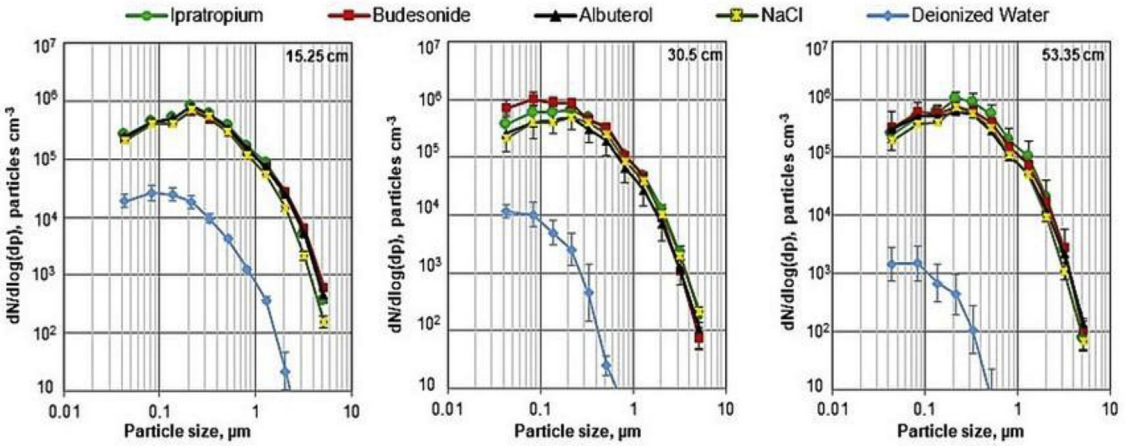

Fig. 3. Particle size distributions obtained from the four selected aerosolized medications and deionized water measured in the breathing zone of an HHCW at different distance from the source (15.25 cm, 30.50 cm and 53.35 cm). Each point represents the geometric mean value of three replicates and the bars represent the geometric standard deviation.

3. Results and discussion

Fig. 3 presents the particle size distributions measured in the breathing zone of the HHCW-simulating manikin for four selected aerosolized medications and deionized water and for the three tested proximities from the source. The aerosol concentrations measured across the particle size range for all four medications and all three distances were significantly higher than background controls (exceeding controls by one to four orders of magnitude). The difference increased with the particle size. The vast majority of aerosol particles (by number) fell in the submicrometer range, while the particle fractional mass distribution for all four medications and three tested distances shifted from this range to considerably above 1 µm. The mass exceeded that of deionized water by seven to eleven orders of magnitude, depending on the particle size. The mass-based inhalation exposure level of the HHCW manikin to the background control aerosol was negligible compared to any aerosolized medication at any distance.

Fig. 3 shows similarity in the particle size distribution among the four selected aerosolized medications at a fixed distance from the source across the tested particle size range ($p > 0.05$). The only exception is Budesonide at 30.50 cm, in which case the size distribution curve was found to differ from the others at a borderline level of significance ($p \approx 0.05$) and mostly due to divergence in the left tail of the distribution (ultrafine particle fraction ≤ 100 nm). When the same comparison was performed for particles above 100 nm, no significant difference was found for this selected range ($p > 0.05$).

Table 1 presents the MMAD and δ_g values calculated for all tested substances based on the size-selective aerosol measurements conducted at different distances. It is seen that MMAD determined for the four aerosolized medications fell in a wider range at the shortest tested distance from the source reaching 2.72 µm for Budesonide. At the same time, the range of MMAD was narrower at greater distances (1.23–1.93 µm at 30.50 cm and 1.46–1.83 µm at 53.35 cm), suggesting that the nebulizer-aerosolized droplets lost most of their water content due to evaporation in the initial phase of their motion. The particles generated from deionized water were much smaller resulting in MMAD of 0.77 µm in proximity to the source and plateauing at ~0.3–0.4 µm at greater distances (~30–50 cm) from the source. The σ_g values were almost the same for different aerosolized medications and different distances. The distributions of particles aerosolized from deionized water were characterized with the lowest σ_g values at the three distances.

ANOVA revealed that there were no significant effects of distance on the particle size distribution (by number) for the four aerosolized medications. However, when the same database was used to calculate the particle fractional mass distribution, the result was different: the distance had a significant effect except for NaCl. This finding may be attributed to evaporation of water – an effect

Table 1
Mass median aerodynamic diameter (MMAD) and geometric standard deviation (δ_g) for the five tested nebulizer-generated aerosols.

Substance	MMAD (µm)			σ_g		
	Distance (cm)			Distance (cm)		
	15.25	*30.50*	*53.35*	*15.25*	*30.50*	*53.35*
Ipratropium Bromide	2.05	1.52	1.46	2.26	2.23	2.13
Budesonide	2.72	1.23	1.83	2.30	2.18	2.26
Albuterol	1.89	1.93	1.63	2.22	2.17	2.22
NaCl	1.63	1.64	1.51	2.17	2.23	2.13
Deionized water	0.77	0.31	0.37	2.00	1.67	1.73

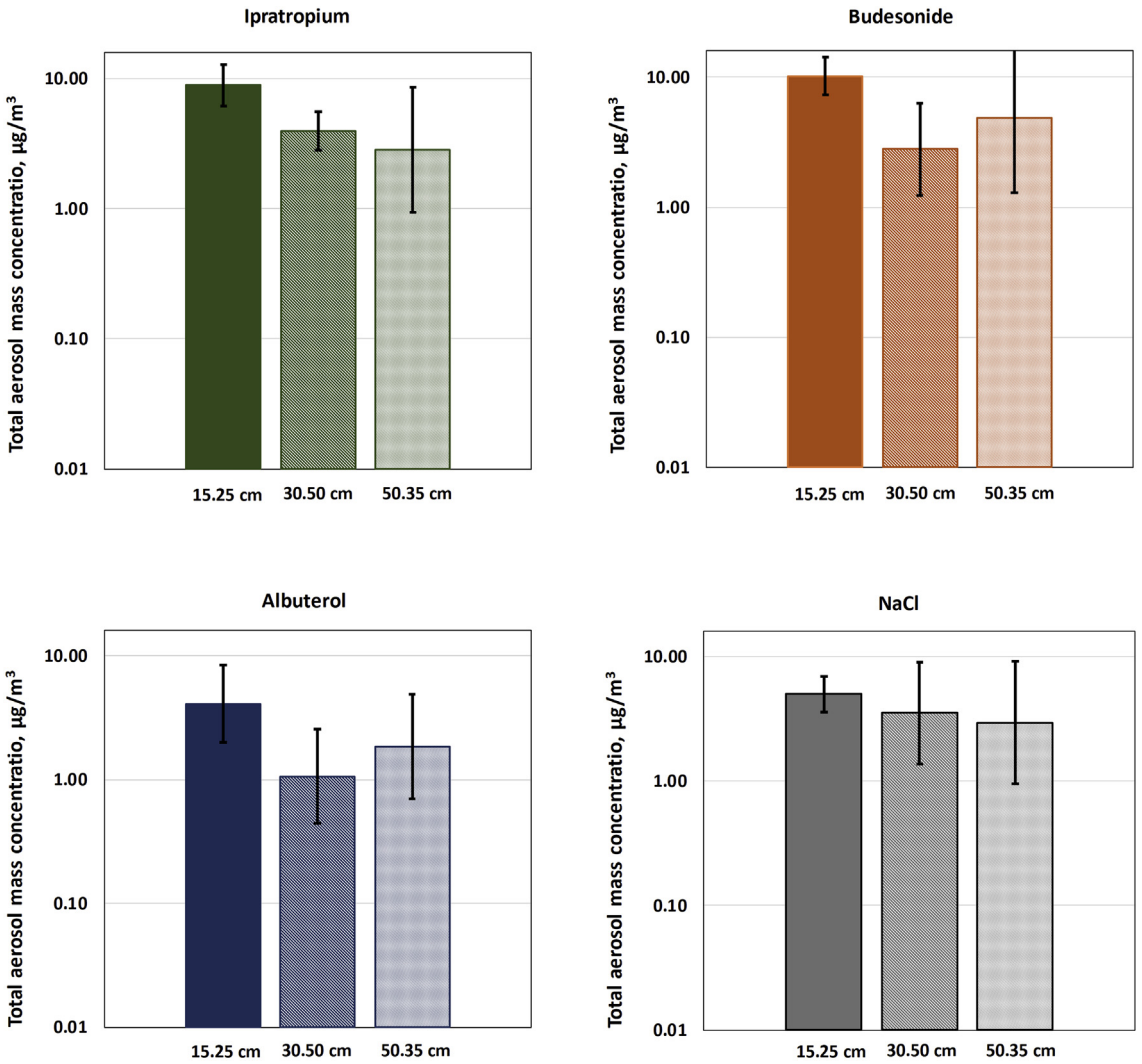

Fig. 4. Total aerosol mass concentration calculated for each of the four aerosolized medications in the breathing zone of an HHCW at different distance from the source (15.25, 30.50 and 53.35 cm). Each point represents the geometric mean value of three replicates and the bars represent the geometric standard deviation.

which is more pronounced for larger particles. It is acknowledged that droplets containing the aerosolized medications such as Ipratropium Bromide, Budesonide and Albuterol may have different evaporation rates than those generated from the saline suspension. The above considerations are consistent with the theoretical estimation of evaporation rate and the time needed for the complete evaporation of a droplet, which we conducted following conventional models described in Hinds (1999) and Kulkarni et al. (2011). The evaporation time was found to be below 1 s, which allows for some unevaporated liquid content in the particles traveling between 6 and 21 inches from the source.

Fig. 4 presents the total aerosol mass concentration determined for each of the four aerosolized medications at different distances. The total mass concentration calculated for particle size distributions fell between 2.29 µg/m^3 (for Albuterol at 30.50 cm) and 10.2 µg/m^3 (for Budesonide at 15.25 cm), depending on the medications and distances. In spite of this wide range, ANOVA revealed there were no significant differences in the total mass concentrations among the four tested aerosolized medications, including (NaCl) within the three distances ($p > 0.05$). Based on the above findings, we concluded that a NaCl suspension can serve as an adequate surrogate for at least three of the tested nebulizer-generated medications for simulating inhalation exposure.

ANOVA also revealed that there was a significant effect of the distances on the total mass concentrations of the tested aerosolized medications ($p < 0.05$), except for Budesonide for which only a borderline significance ($p = 0.05$) was identified. Pairwise comparison (Tukey's HSD) among the four aerosolized medications showed a significant effect of distance when it increased from 15.25 cm to 30.50 cm and from 15.25 cm to 53.35 cm ($p < 0.05$) but did not reveal the same significance between 30.50 cm and 53.35 cm ($p > 0.05$). One reason could be that the particle mass, which decreases with distance due to evaporation, reaches a plateau at around ~30 cm.

4. Study limitations

This pilot study was limited to one brand of aerosol delivery system and four aerosolized medications. Therefore, the obtained data may not be fully representative of all other aerosol delivery systems and all other aerosolized medications that are used by HHCWs treating patients at their homes. However, the configuration is commonly used in the home setting. Additionally, mouthpieces are available for medical nebulizers (as compared to the mask we used in this pilot study); the mouthpiece configuration may affect characteristics of the generated aerosol. Masks tend to be used in pediatric patients and in older adults who may be particularly ill and unable to hold a mouthpiece in their mouth. Therefore, use of a mask is a common scenario in certain patient populations. The dimensions of the test chamber designed for this investigation were chosen to fit the chamber inside the biosafety cabinet. This limited the size of the chamber, which presented a challenge in accommodating two manikins at the greatest tested distance, 53.35 cm. As a result, the HHCW- simulating manikin was close to the chamber's border allowing for some boundary effects on the measured aerosol. Turbulence caused by an additional air flow diversion near that manikin may have caused an increase in the aerosol concentration. Even considering the above limitations, this study generated useful results with respect to the potential inhalation aerosol exposure of HHCWs treating patients with nebulizer-aerosolized medications.

5. Conclusion

Our results obtained in this pilot simulation study for four common nebulizer-aerosolized medications and three distances from the source show that inhalation aerosol exposure of HHCWs is significant as compared to controls across the tested particle size range. The particle size distributions measured for the four aerosols at a fixed distance from the source demonstrated similar trends with no significant differences identified in most cases. No significant effect of the distance from the aerosol delivery point on the particle size distribution was identified; however, the particle mass distributions were generally affected by the distance. While the total aerosol mass concentration in the breathing zone of the simulated HHCW ranged widely, from 2.29 to 10.2 $\mu g/m^3$, it was not significantly affected by medication type; therefore, we concluded that NaCl can serve as a surrogate of the selected nebulizer-administered drugs.

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