In Vitro Comparison of Aerosol Delivery Using Different Face Masks and Flow Rates With a High-Flow Humidity System

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BACKGROUND: Aerosol drug delivery to infants and small children is influenced by many factors, such as types of interface, gas flows, and the designs of face masks. The purpose of this in vitro study was to evaluate aerosol delivery during administration of gas flows across the range used clinically with high-flow humidity systems using 2 aerosol masks. METHODS: A spontaneous lung model was used to simulate an infant/young toddler up to 2 y of age and pediatric breathing patterns. Nebulized salbutamol by a vibrating mesh nebulizer positioned at the inlet of a high-flow humidification system at gas flows of 3, 6, and 12 L/min was delivered via pediatric face masks to a pediatric face mannequin attached to a filter. Aerosol particle size distribution exiting the vibrating mesh nebulizer and at the mask position distal to the heated humidifier with 3 flows was measured with a cascade impactor. Eluted drug from the filters and the impactor was analyzed with a spectrophotometer ($n = 3$). Statistical analysis was performed by analysis of variance with a significant level of $P < .05$. RESULTS: The inhaled mass was between 2.8% and 8.1% among all settings and was significantly lower at 12 L/min ($P = .004$) in the pediatric model. Drug delivery with pediatric breathing was greater than with infant breathing ($P = .004$). The particle size distribution of aerosol emitted from the nebulizer was larger than the heated humidified aerosol exiting the tubing ($P = .002$), with no difference between the 3 flows ($P = .10$). CONCLUSIONS: The flows of gas entering the mask and breathing patterns influence aerosol delivery, independent of the face mask used. Aerosol delivery through a high-flow humidification system via mask could be effective with both infant and pediatric breathing patterns. *Key words: pediatric; aerosol delivery; high-flow humidification; aerosol mask; gas flows; particle size distribution; vibrating mesh nebulizer.* [Respir Care 2015;60(9):1215–1219. © 2015 Daedalus Enterprises]

Introduction

Aerosol therapy along with oxygen therapy is often administered to hospitalized infants and children. Chua et al[1] reported lung deposition of 0.3–1.6% in sleeping infants from 0.3 to 1.4 y of age using a jet nebulizer operating at 9 L/min. However, administering aerosol therapy to infants and children is a challenge, as the device noise, mask fit, and cold air can irritate these small patients, causing

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various degrees of distress associated with decreased aerosol delivery.[2]

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High-flow, heated humidified oxygen therapy provides oxygen gas flows higher than the patient's inspiratory flow, and also provides adequately warmed and humidified gas to conducting airways to reduce airway damage associated with gas conditioning. Aerosol therapy through the high-flow nasal cannula has been suggested as a reasonable interface option for aerosol administration, with an inhaled dose comparable to standard aerosol therapy that is well tolerated by the child.[3,4] In vitro studies have shown the efficiency of delivering bronchodilators via high-flow nasal cannula, but the inhaled dose decreased significantly as the flow increased.[3-5] Although clinicians have adopted such technology, the question arises: how much aerosol would be inhaled using a similar setup with an aerosol face mask? Studies have shown that the design of the face mask affects the amount of aerosolized drug delivery.[6-8] The deposition of aerosolized drug delivered with a face mask through a high-flow heated humidified oxygen system has not been examined.

The purpose of this in vitro study was to compare the efficiency of aerosol delivery with 2 different face mask designs using a high-flow humidity system and variable gas flows. We hypothesize that the inhaled dose will be inversely related to flow through the system, with differences between infant and pediatric breathing patterns.

QUICK LOOK

Current knowledge

Aerosol drug delivery to infants and small children can be influenced by a number of factors including the type of interface, gas flow, and the face mask design. The presence of humidity can also alter aerosol delivery. Previous research suggests that humidity can both facilitate and interfere with aerosol deposition.

What this paper contributes to our knowledge

Aerosol delivery with high-flow humidification is affected by gas flow and breathing patterns, independent of the face mask used. Gas flows > 12 L/min decreased the inhaled drug delivered. During aerosol delivery through a high-flow humidification system via mask at flows > 12 L/min, medication dose may need to be increased to achieve the desired effect.

Methods

This study was conducted in the Respiratory Research Laboratory in the Respiratory Therapy Department at Chang Gung University (Taoyuan, Taiwan, Republic of China).

Lung Model

A lung simulator (ASL 5000, IngMar Medical, Pittsburgh, Pennsylvania) was set to represent spontaneous breathing patterns for an infant/young toddler up to 2 y of age (weight range 10–15 kg) and for a child (weight range 25–30 kg) . Infant/young toddler breathing pattern parameters were set at tidal volume = 100 mL, inspiratory time = 0.7 s, and breathing frequency = 30 breaths/min, and pediatric parameters were tidal volume = 250 mL, inspiratory time = 1.0 s, and breathing frequency = 20 breaths/min. To represent drug deposition distal to the upper airway, a face and anatomical upper airway of a child cardiopulmonary resuscitation mannequin was attached distal to the hypo-pharynx to a bacterial filter (GaleMed, Taipei, Taiwan, Republic of China) with a filtration rate > 99.999% at particle size of 0.3 μm, and with an internal dead space of 33 mL. Figure 1 shows the configuration of the experimental design.

Inhaled Dose Measurements

A unit-dose of salbutamol (5.0 mg/2.5 mL; GlaxoSmithKline, Philadelphia, Pennsylvania) was placed in the reservoir of a vibrating mesh nebulizer (VMN; Aeroneb Solo, Aerogen, Mountain View, California) with continuous aerosol generation. The VMN was run until 30 s after no generated aerosol was visible. Each experiment was repeated in triplicate. Results were expressed as the proportion of the dose delivered distal to the airway.

Compressed air from a central piping system at 50 psi was metered through a pressure compensated flow meter at 3, 6, and 12 L/min, passing through a 22 mm T-adapter holding the VMN and attached to the inspiratory inlet of the heated humidifier (MR410, Fisher & Paykel, Auckland, New Zealand). The temperature control of the MR410 humidifier was a scale of 1–9, and the maximum setting (9) was set in the present study. The delivered temperature with set flows was approximately 34–35°C.

A heated wire circuit from the humidifier was attached to an OxyKid aerosol mask (SouthMedic, Barrie, Ontario, Canada) and the Dragon aerosol mask (Cardinal Health, Dublin, Ohio). Figure 2 demonstrates the configuration of the 2 masks. Both aerosol masks offer child-friendly elements to improve compliance, with substantial difference in design. The OxyKid is a front-loaded mask with gas directed to the face at a 90° angle with 3 large holes on

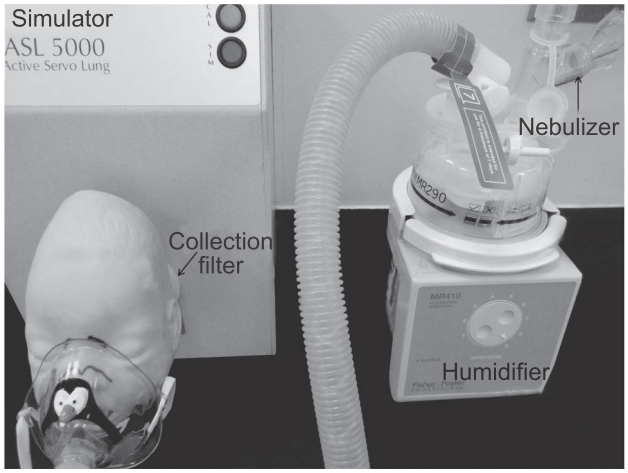

Fig. 1. Configuration of the experimental design.

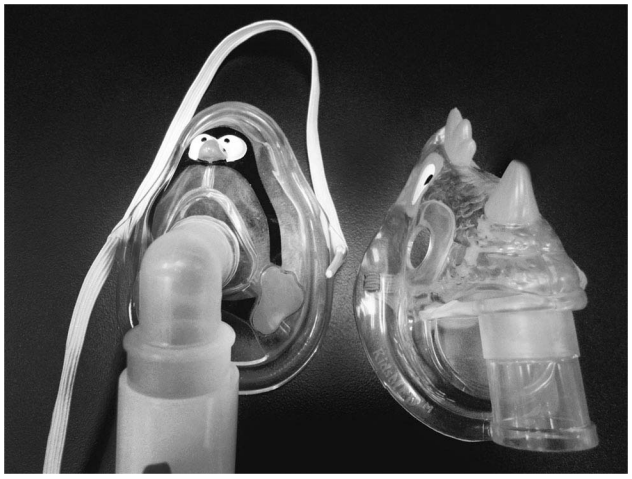

Fig. 2. The OxyKid mask (left) and the Dragon mask (right).

both sides and the bottom. In contrast, the Dragon mask is a bottom-loaded design that directs the aerosol and gas flow up to the face from below the nose, with smaller 1 cm side-holes that somewhat restrict gas entering or leaving the sides of the mask. The same size mask was used with both sets of breathing parameters.

Particle Size Measurement

Aerosol generated from the VMN was characterized using an Anderson cascade impactor (Thermo Fisher Scientific, Waltham, Massachusetts) to measure aerosol particle size distribution in accordance with United States pharmaceutical standards, at a flow of 28.3 L/min. Aerosol was sampled as it was emitted from the VMN at ambient condition, and after passing through the humidifier and the heated tubing at the position of the mask with flows of 3, 6 and 12 L/min. All measurements were repeated in triplicate.

Drug Measurement

Drug collected on the filter and impactor stages was eluted with distilled water for 1 min with gentle agitation and analyzed with a spectrophotometer (Thermo Fisher Scientific) with wavelength at 276 nm. The spectrophotometer was calibrated and set to zero before each trial. The concentration of the sample solution and the amount of drug were calculated from a known concentration/absorbency regression ($r^2 > .99$).

Data Analysis

The amount of drug eluted from the filter was quantified in μg/mL and expressed as a percentage of the total dose placed in the VMN. The median mass aerodynamic diameter (MMAD) and the geometric standard deviation (GSD) were calculated from the amount of drug deposited on the impactor plates and the throat. The normality of data distribution was analyzed. The mean ± SD was calculated for each component of the drug mass eluted from the inspiration filter. Statistical analyses were performed using SPSS 18.0 (SPSS, Chicago, Illinois). Independent *t* test and one-way analysis of variance with Bonferroni test were used for statistical analysis, and $P < .05$ was used for statistical significance. To test our hypothesis that the inhaled dose was inversely related to flow through the system, Pearson correlation analysis was used.

Results

Inhaled Drug

Inhaled drug delivered expressed as percentage (mean ± SD) of total dose in the infant/young toddler model is shown in Table 1. The inhaled mass in the OxyKid mask was between 2.8% and 7.3%, and it was significantly lower at 12 L/min than at 3 and 6 L/min ($P = .004$). Drug deposition with the Dragon mask was 3.2–8.1% with a significant difference ($P = .003$) in the pediatric model. The inhaled mass with the Dragon mask under the infant/young toddler breathing pattern was significantly greater at 6 L/min than at 12 L/min ($P < .001$). Drug delivery with the pediatric breathing pattern was greater than infant/young toddler pattern with a mean ± SD of 6.4 ± 1.8% versus 4.6 ± 1.5%, respectively ($P = .004$). Inhaled dose was similar with OxyKid and Dragon masks (mean ± SD of 5.0 ± 1.8% and 6.0 ± 1.9%, respectively, $P = .12$).

The correlation between the inhaled mass and flow showed $r^2 = .39$ ($P < .001$). The regression equation showed a negative relationship between inhaled mass and flow ($Y = 7.786 - 0.328 \times \text{flow}$).

Table 1. Inhaled Mass, With Both Infant and Pediatric Breathing Patterns, at Flows of 3, 6, and 12 L/min

Model	Mask and Flow					
	OxyKid			Dragon		
	3 L/min	6 L/min	12 L/min*	3 L/min	6 L/min	12 L/min*
Infant	6.4 ± 1.2	4.2 ± 0.74	2.8 ± 0.16	4.7 ± 0.82	6.2 ± 1.38	3.2 ± 0.44
Pediatric	7.3 ± 0.9	5.8 ± 0.62	3.4 ± 0.36	8.0 ± 1.09	8.1 ± 1.12	5.7 ± 021

Inhaled mass was expressed as percentage (mean ± SD) of total dose inhaled with the 2 masks.
* Drug delivery with 12 L/min was less than other 2 flows ($P < .05$).

Table 2. Aerosol Particle Size Distributions Expressed as MMAD and GSD of Nebulizer Output and Mask Output at 3, 6, and 12 L/min

	Distributions				*P*
	Nebulizer	3 L/min	6 L/min	12 L/min	
MMAD (μm)	4.0 ± 0.14*	2.8 ± 0.12	3.3 ± 0.15	2.8 ± 0.36	.002
GSD (μm)	2.1 ± 0.06	1.7 ± 0.2	1.9 ± 0.25	1.7 ± 0.15	.06

Aerosol particle size distributions are expressed as MMAD and GSD.
* Greater than output from mask at all 3 flows ($P < .002$).
MMAD = median mass aerodynamic diameter
GSD = geometric SD

Aerosol Particle Size Distributions

Aerosol characterizations with the MMAD and GSD are presented in Table 2 for measurements at the exit of the VMN at ambient conditions, and with the 3 flows after passing through a heated humidifier and delivery tubing. The MMAD of aerosol emitted from the VMN was larger than the heated humidified aerosol exiting the tubing at 3, 6, and 12 L/min ($P = .002$) with no difference between the 3 flows ($P = .10$).

Discussion

Our results confirmed that variation of flow to a mask influences aerosol drug deposition. In general, the higher the flow delivered, the less aerosol delivered to the patient, although we did see an exception with increased or similar drug delivery at 6 L/min as opposed to 3 L/min with the Dragon mask with infant/young toddler and pediatric breathing patterns, respectively. Drug delivery through a mask is also influenced by breathing pattern; the lower the tidal volume and minute ventilation, the less aerosol delivered to the patient. In contrast, delivered MMAD was not affected by changes in delivered flow.

Comparing our model to a similar lung model by Ari et al[3] on the influence of flow through the high-flow nasal cannula, as the total flow increases, the inhaled dose decreases. The inhaled dose was approximately 5-fold higher with an oxygen flow of 3 L/min than with 6 L/min. A major difference between delivery via nasal prongs and the aerosol mask may be the size of reservoir represented by the nasopharynx and the volume of the mask. Our results showed that the inhaled dose was decreased significantly only at 12 L/min. With an infant/young toddler breathing pattern, the drug delivery was 10.6% with nasal cannula and 6.5% with mask at 3 L/min. This suggests that aerosol delivery can be more efficient with a nasal cannula at lower flows. However, as the flow increases, a mask interface may be more efficient for aerosol delivery.

In children, aerosol delivery with a jet nebulizer is influenced by the design of the aerosol mask.[6,7,9,10] Harris and Smaldone[10] demonstrated that, as an accessory for a jet nebulizer, the front-loaded mask configuration was more efficient than the bottom-loaded mask configuration, which is in contrast to our study. Our data showed that the designs of the face masks we tested do not influence aerosol delivery with a VMN at the flows tested. A jet nebulizer requires a gas source of 50 psig at 6–10 L/min. As the aerosol generated by a jet nebulizer travels to the attached device, the first impaction may influence drug deposition.

A study by Smaldone et al[11] has suggested increased particle inertia along the edge of the mask influences drug deposition. They suggested a difference between front and bottom loading mask designs. However, with a VMN, the exit velocity of the aerosol is low (<4 m/s). In our study, the VMN was placed upstream of the heated humidifier system. With the humidifier as a reservoir and first-line baffle, the effect of particle inertia was less evident; thus,

the drug deposition was similar with 2 different aerosol masks.

Our results of reduced particle size distribution between nebulizer output and aerosol leaving the heated tubing are consistent with reports from Bhashyam et al[4] using 3 L/min. However, we did not see a further reduction in particle size with the higher flows tested (6 and 12 L/min), suggesting that particle size is reduced but not flow-dependent in the range tested.

Limitations

This was an in vitro model that simulated the breathing pattern of infant/young toddlers up to 2 y of age and small children. Pediatric patients range from preterm infants to youth 18 y of age with different ranges of tidal volume and breathing patterns. Inhaled mass may vary with these parameters. Additionally, the aerosolized drug was captured and measured at the position of the mouth with no simulation of upper airway deposition. Clinical trials are needed to verify and correlate in vitro differences to the physiological and clinical effects of aerosol delivery through high-flow humidification system in patients.

Conclusions

Aerosol delivery with high-flow humidification is affected by the flows of gas entering a mask and the breathing patterns, independent of the face mask used. As gas flow increased to 12 L/min, the inhaled drug delivered decreased. Based on this in vitro study of aerosol delivery through a high-flow humidification system via mask, clinicians may want to consider increasing doses when administering higher flows.

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