Total Drug Delivery Comparison using the Adult Amsino OneMask™ and Predicate Mask from Southmedic on a Ventilated Human Model

Abstract

This in vitro study compares the amount of total drug delivery of a new mask device to that of a predicate when connected to a ventilated human model. The objective is to compare the total inhaled mass of nebulized albuterol sulfate using the Amsino OneMask™ and the predicate masks for two adult respiratory models. The predicates were chosen based on similar open-mouth design. Each mask was tested in triplicate using two different ventilator respiratory models based on International Commission on Radiological Protection (ICRP) models.

The model compares the Amsino OneMask™ (Amsino International, Inc., Pomona, CA) to that of a commercially available mask: the Southmedic OxyMulti Mask (Southmedic, Barrie, Ontario Canada).

The mannequin for the adult model was a Prestan Adult CPR-AED Manikin (PP-AM-100M-MS). The mannequin was modified with a throat tube insert and connected to an enclosed 47 mm sample filter using Whatman 934-AH glass micro fiber 47 mm filters. The ventilator used for simulating the various respiratory conditions was a Philips Respironics Life-Care PLV-100 (Andover, MA). Two different respiratory parameters were used for the testing of the masks. The masks were tested with respiratory parameters corresponding to the ICRP model for adult male resting and adult female resting conditions. Each mask was tested in triplicate to achieve a 95% confidence level of testing.

Ventolin Nebules, 2.5mg / 2.5 ml salbutamol sulfate (racemic albuterol, albuterol sulfate), inhalation solution was nebulized with a widely used jet nebulizer, the Hudson RCI micro-mist nebulizer (Research Triangle Park, NC). In each trial the nebulizer was filled with 5 ml dose of Albuterol sulfate solution (2 Nebules) and powered with oxygen at 8 L/min with a total treatment time of 5 minutes. Analysis of drug content was performed by HPLC on a Dionex Ultimate 3000 nano HPLC, equipped with Dionex UVD-3000 UV/VIS detector (Thermo Scientific, Sunnyvale, CA).

Introduction

Both the Amsino OneMask™ and Southmedic OxyMulti Mask are combination devices that allow for the delivery of aerosolized medication via nebulizer while providing oxygen therapy. Each mask features an open-port mouth design to allow the patient comfort and the ability to imbibe food, liquid, or oral dose medication without removal of the mask. The Southmedic has a mouth opening and additional port opening on either side of the mask. The purpose of the present study was to determine the total inhaled drug mass, patient delivery rate, nebulizer residual drug, and estimated ambient drug loss during delivery of nebulized albuterol sulfate to both the newly proposed Amsino OneMask™ and Southmedic predicate. Figure 1 shows pictures of each mask and some key features of each mask design.

Adult Masks

Mask Features	Picture	
		
Manufacturer	Amsino	Southmedic
Model	OneMask	OxyMulti
Length (cm)*	12.7	11.1
Width (cm)*	7.9	6.7
Mask Volume (ml)**	115	107
Surafce Area of Openings (cm^2)*	7.2	24.3

* Mask dimesions and openings are approximate due to irregular design

** Mask volume measured by filling mask with water

Figure 1: General *features of the tested aerosol masks.*

Study Design

The study was designed to evaluate the devices utilizing a jet nebulizer on a simulated patient breathing model. The breathing model consisted of modified CRP mannequins equipped with throat tubes to an absolute filter. Various respiratory parameters were tested to compare the vented design of Amsino OneMask™ delivery to that of the Southmedic delivery under identical breathing conditions. The testing platform utilizes a Philips Respironics Life-Care PLV-100 (Andover, MA) piston ventilator integrated to a CPR mannequin equipped with an absolute filter to serve as the patient model. The mask was placed onto the mannequin and the ventilation parameters were set.

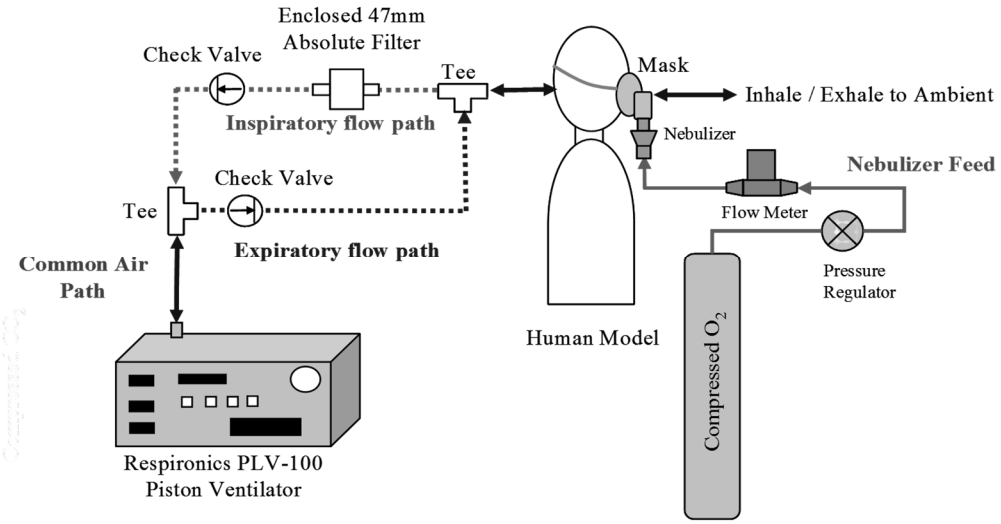


Figure 2: *Flow Diagram for Drug delivery via simulated human respiration model*

.

Adult Mask Testing Matrix

	Device Parameters						Respiratory Parameters				
Test	Mask	Type	Nebulizer Flow (lpm)	Dose	Drug	Time	Respiratory model	Frequency (bpm)	Tidal Volume (L)	I:E Ratio	Trials
1	Amsino OneMask	Adult	8	5ml	Albuterol Sulfate (2.5mg/2.5ml)	5 min	Male, resting	12	0.75	1:2.9	triplicate
2	Southmedic OxyMulti	Adult	8	5ml	Albuterol Sulfate (2.5mg/2.5ml)	5 min	Male, resting	12	0.75	1:2.9	triplicate
3	Amsino OneMask	Adult	8	5ml	Albuterol Sulfate (2.5mg/2.5ml)	5 min	Female, resting	14	0.48	1:2.8	triplicate
4	Southmedic OxyMulti	Adult	8	5ml	Albuterol Sulfate (2.5mg/2.5ml)	5 min	Female, resting	14	0.48	1:2.8	triplicate

Table 1: *Test Matrix and Respiratory Parameters for each trial.*

The nebulizer was filled using two (2) Ventolin Nebules, 2.5mg / 2.5 ml salbutamol sulfate IP (total volume 5 ml per trial). The jet nebulizer was weighed before fill, after fill and post-test to determine overall mass balance of the system. After nebulizer fill and positioning onto the mannequin the ventilator was initiated. Oxygen feed to the jet nebulizer was initiated (8 L/min) and allowed to run for 5 minutes.

After the trial, the sample filter was collected and extracted in mobile phase along with the residual Albuterol sulfate remaining in the nebulization cup. Figure 1 shows the flow diagram for the testing.

Respiratory Model

Respiratory parameters for all testing were selected based upon the ICRP respiratory parameters for male and female resting for the adult mask models. These respiratory parameters (shown in table 1) were used to program the Respironics PLV-100 piston ventilator.

Figure 3: Adult *Mannequin with Adult Amsino OneMask™.*

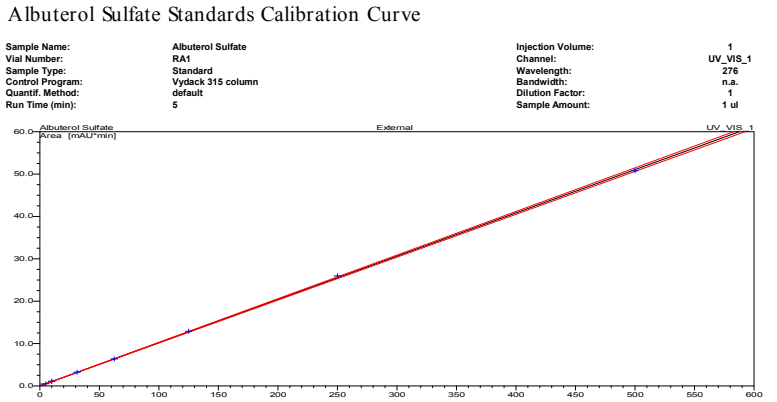
Sample Collection

Filter samples were collected using enclosed 47 mm sample filter using Whatman 934-AH glass micro fiber 47 mm filters. All filter samples were placed in a 15ml falcon tube and extracted in 3,000 ul mobile phase. The filter samples were then filtered using a syringe equipped with a 0.45um nylon syringe filter. All nebulizer samples were diluted with mobile phase at a 1:9 dilution before being analyzed. After filter and nebulizer extraction the samples were analyzed via HPLC for the Albuterol content. Total drug delivery, estimated ambient drug loss, patient drug delivery rates and delivery efficiencies were calculated for each trial and compared. All testing was performed in triplicate for each mask, for both the Amsino OneMask™ and Southmedic masks, at two different respiratory parameters for a total of 12 independent trials.

Drug Analysis

All drug content analysis was performed using a Dionex Ultimate 3000 nano-HPLC equipped with a Dionex UVD-3000 multi-wavelength UV/VIS Detector using a micro flow cell (75um x 10mm path length, total analytical volume 44.2 nl). The column used was a Vydac 238DE5.315 (0.3um ID x 150mm) C18 monomeric, 100A (USP L1) column with a column flow rate of 10ul/min at a nominal pressure of 206 bar. Sample injection was performed with a 1 µl sample loop in full loop injection mode. Detection was with UV at 276nm. Data acquisition and analysis were performed using Chromeleon 6.8 SR11 Build 3161 with GLP compliance client features installed.

US Pharacopia monograph USP29nf24s_m1218 was followed as a reference method for analysis of albuterol sulfate. Briefly, the method involved dilution of an appropriate formulation of albuterol sulfate in mobile phase; 60% buffer and 40% methanol (Acros Organics, HPLC grade methanol, lot # 1154574). Buffer formulation contains reverse osmosis filtered de-ionized water with 1.13gr of sodium 1-hexanesulfonate (Alfa Aesar, Sodium 1-hexanesulfonate, lot # 10159201) in 1200 ml of water, with 2 ml glacial acetic acid (Acros Organics, Acetic Acid for analysis, lot # A0317484) added.



No.	Peak Name	Cal.Mode	Cal.Type	Offset	Slope	RF-Value	Std.Dev.	R-Square %
1	Albuterol Sulfate	Total	Lin	0	0.09300	10.709	0.074	99.998

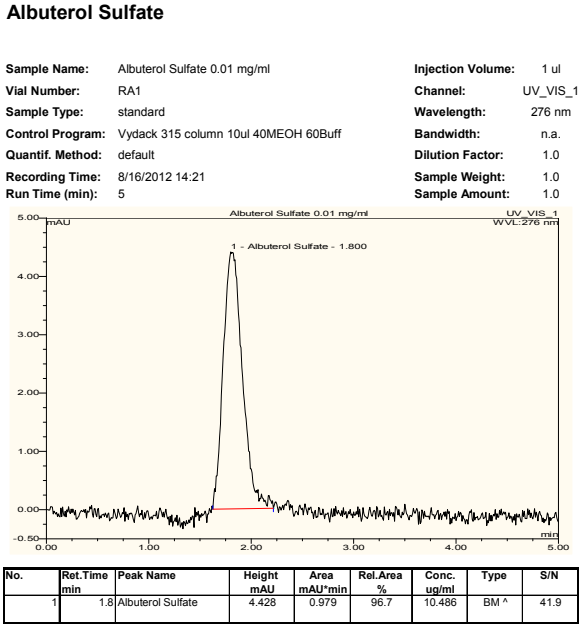
No.	Name	Sample Type	Pos	Inj.Vol. µl	Ref. Amount Set (ug/ml)	Concentration ug/ml UV_VIS_1	Peak Start Code UV_VIS_1	Signal:Noise UV_VIS_1
1	Albuterol, 0.001 mg/ml	standard	RA1	1.0	1	1.0275	B	3.2
2	Albuterol, 0.005 mg/ml	standard	RA2	1.0	5	5.1268	B	14.7
3	Albuterol, 0.01 mg/ml	standard	RA3	1.0	10	10.6717	B	41.9
4	Albuterol, 0.03125 mg/ml	standard	RA4	1.0	31.25	31.8349	B	94.9
5	Albuterol, 0.0625 mg/ml	standard	RA5	1.0	62.5	62.3909	B	188.7
6	Albuterol, 0.125 mg/ml	standard	RA6	1.0	125	126.3855	B	283.5
7	Albuterol, 0.25 mg/ml	standard	RA7	1.0	250	254.3209	B	466.5
8	Albuterol, 0.5 mg/ml	standard	RA8	1.0	500	500.2844	B	762.8

Figure 4: *Albuterol Sulfate Calibration Standards and Linear Regression showing 95% confidence levels (red).*

The mobile phase solution was mixed and filtered through a 0.45um filter membrane. The final mobile phase is a 60:40 dilution of Buffer:MEOH.

Standard preparation includes making a stock concentration of 500µg/ml of Albuterol Sulfate in mobile phase. The stock concentration was diluted to make a 6-point serial dilution for use as calibration standards for Albuterol sulfate determination in unknown samples. The concentrations of the standards used are: 10, 31.25, 62.5, 125, 250 and 500 µg/ml Albuterol sulfate in mobile phase.

The calibration curve was plotted for peak area of the analyte against the corresponding concentrations, which is obtained using linear regression (with forced zero intercept) analysis within Chromeleon 6.8. The corresponding linear calibration curve was y = 0.09300x with a correlation coefficient (R-squared) of 0.99998. The results showed an excellent linearity across the entire calibration standard range. Figure 4 shows the linear calibration curve generated in Chromeleon with 95% confidence levels in red.



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Conc. ug/ml	Type	S/N
1	1.8	Albuterol Sulfate	4.428	0.979	96.7	10.486	BM ^	41.9

Figure 5: *Typical Chromatogram for Albuterol Sulfate (shows strong signal at 10µg/ml detection levels).*

Figure 5 shows a typical chromatogram for albuterol sulfate. The sample shown has a concentration of 10 µg/ml and shows a strong peak with a Signal-to-Noise ratio of 41.9. Sample drug

content was computed by multiplying concentration, total sample volume, and dilution factor for all unknown samples.

Limit of Detection and Limit of Quantification

The sensitivity of the method was determined using two different accepted methods for determining limits of detection (LOD) and the quantification (LOQ). The first method is based on the standard deviation of the response and the slope as described in ICH guidelines Q2 (R1) (ICH, 2005). The LOD and LOQ were calculated according to the following equation:

$$LOD = 3.3\ \sigma / S;\ LOQ = 10\ \sigma / S$$

Where σ=the standard deviation of the response; S = slope of the calibration curve. The LOD and LOQ were found to be 2.38 µg/ml and 7.97 µg/ml, respectively, using this method.

A second method to determine LOD and LOQ was examined. Samples with signal-to-noise ratios corresponding to 3 are accepted as LOD and samples with signal-to-noise ratio values of 10 are accepted as LOQ values.

Prepared samples with 1 µg/ml and 5 µg/ml of albuterol sulfate were analyzed. The 1 µg/ml prepared standard showed a signal-to-noise ratio of 3.2 while a 5ug/ml prepared standard showed a Signal-to-Noise ratio of 14.7. Using signal-to-noise ratio to determine effective LOD and LOQ values yield a sub 1 µg/ml LOD and a sub 5 µg/ml LOQ.

Statistical Analysis

Mean and standard deviation were calculated for all trials for each component of: total delivered drug mass, nebulizer drug fill, nebulizer drug recover, estimated ambient loss, patient drug delivery rates and delivery efficiencies.

Results

Results show that the new Amsino OneMask™ Adult Oxygen Mask outperformed the Southmedic OxyMulti Mask for both adult respiratory models. The Amsino OneMask™ achieved a 136.0% delivery for the adult male resting respiratory model and 111.2% for the adult female resting respiratory model, when compared to the Southmedic OxyMulti Mask.

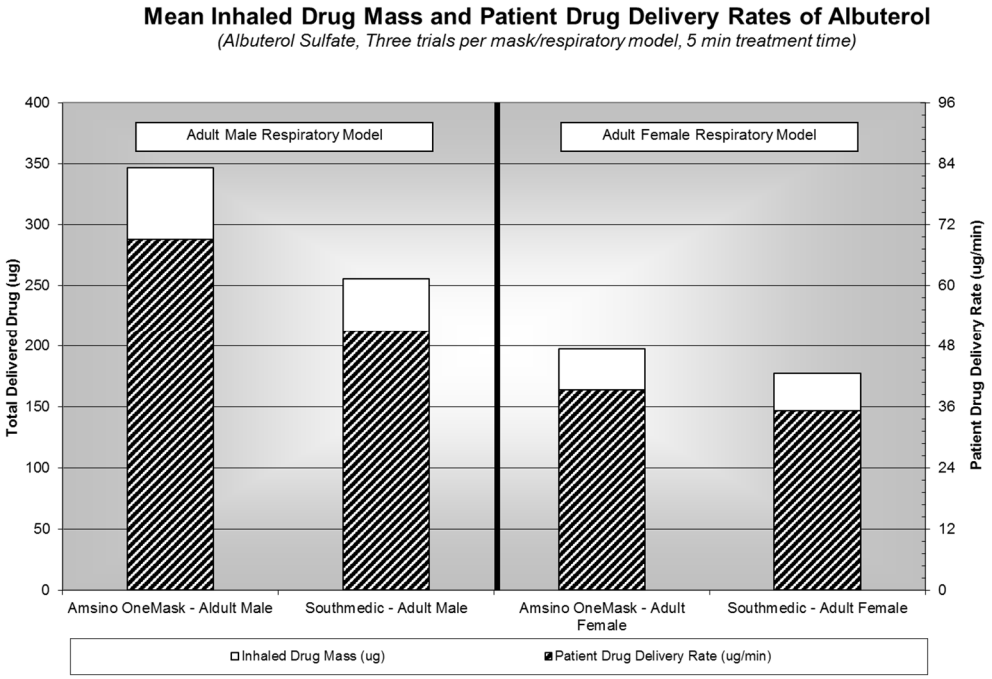


Figure 6: Mean Inhaled Albuterol and Mean Patient Delivery Rates.

Adult Mask Testing Summary

Features	Respiratory Model	New Amsino OneMask	Predicate SouthmedicOxyMulti
Nebulizer Fill (ug)	Adult Male, resting	4893.6 +/- 46.8	4827.3 +/- 56.7
	Adult Female, resting	4896.7 +/- 72.6	4859.5 +/- 90.2
Nebulizer Residual (ug)	Adult Male, resting	3449.6 +/- 164.9	3764.1 +/- 88.6
	Adult Female, resting	3798.3 +/- 58.8	3605.7 +/- 140.0
Lost to Ambient (ug)	Adult Male, resting	1097.3 +/- 112.7	807.8 +/- 33.8
	Adult Female, resting	901.4 +/- 49.8	1076. +/- 45.4
Total Delivered Dose (ug)	Adult Male, resting	346.7 +/- 27.0	255.3 +/- 10.2
	Adult Female, resting	196.9 +/- 18.1	177.1 +/- 15.5
Total Delivered Dose Frac (%)	Adult Male, resting	24.0% +/- 0.64%	24.0% +/- 0.59%
	Adult Female, resting	17.9% +/- 1.1%	14.1% +/- 1%
Treatment Time (min)	Adult Male, resting	5.019 +/- 0.02	5.026 +/- 0.00
	Adult Female, resting	5.017 +/- 0.00	5.034 +/- 0.02
Patient Delivery Rate (ug/min)	Adult Male, resting	69.1 +/- 5.5	50.8 +/- 2
	Adult Female, resting	39.3 +/- 3.7	35.2 +/- 3
Confidence level of testing		The test and number of samples (3) tested provide 95% confidence level	

All values Mean +/- SD

Table 2: *Testing Results for all trials (Mean ± SD), N=3.*

Amsino OneMask™ Adult Oxygen Mask and Southmedic OxyMulti Mask for the male respiratory model yielded a total Albuterol patient drug delivery of 346.7µg ± 27.0µg (mean ± SD) versus 255.3µg ± 10.2µg for a 5 minute treatment time. The female respiratory model yielded a total drug delivery of 196.9µg ± 18.1µg for the Amsino OneMask™ mask versus 177.1µg ± 15.5µg for the Southmedic OxyMulti mask.

Figure 6 shows the mean values graphically for all testing for total delivered dose (µg) and patient drug delivery rate (µg/min)

Conclusions

Results show that the newly proposed Amsino OneMask™ Adult Oxygen Mask outperformed the Southmedic OxyMulti Mask for both adult respiratory models for total delivered dose and patient delivery rates. The Amsino OneMask™ Adult Oxygen Mask provided 136.0% delivery when compared with the Southmedic OxyMulti for male respiratory model and 111.2% for the female respiratory model.

Amsino OneMask™ Adult Oxygen Mask and Southmedic OxyMulti Mask for the male respiratory model yielded a total Albuterol patient drug delivery of 346.7µg ± 27.0µg (mean ± SD) versus 255.3µg ± 10.2µg for a 5 minute treatment time. The female respiratory model yielded a total drug delivery of 196.9µg ± 18.1µg for the Amsino mask versus 177.1µg ± 15.5µg for the Southmedic OxyMulti mask for a 5 minute treatment time.

Looking at the delivered dose fractions we can perhaps generate a hypothesis as to why the Amsino outperformed the Southmedic mask. Delivered Dose Fraction is defined as:

$$D_{frac} = \frac{D_{delivered}}{N_{fill} - N_{res}}$$

Where D_{frac} is the delivered dose fraction, $D_{delivered}$ is the delivered dose to the patient, N_{fill} is the initial nebulizer drug fill and N_{res} is the nebulizer residual drug post testing.

The testing for the male respiratory model indicates that both masks had a delivered dose fraction of 24.0%, although, the overall total drug delivery is lower for the Southmedic mask. This is due to the fact that Southmedic mask incorporated a diffuser in-between the nebulizer and the mask. This diffuser is most likely acting as an impaction surface which reduces overall aerosol delivery into the mask.

Looking at the adult female respiratory model the data shows that the delivered dose fraction for the Amsino OneMask™ mask was 17.9% ± 1.1% versus 14.1%± 1.0% for the Southmedic.

It is hypothesized that the decrease in total delivered dose for the Southmedic OxyMulti Mask is most likely due to increased losses to the environment at the reduced breathing rates. This reduced aerosol delivery at lower tidal volumes is most likely due to the fact the Southmedic mask has a substantially greater surface area of open ports, 24.3 cm^2, compared to the Amsino OneMask™ Adult mask with 7.2 cm^2. As tidal volume and breathing rate decreases the Southmedic losses increase.

Overall the study shows that the Amsino OneMask™ Adult Oxygen Mask provides a substantially equivalent total patient delivered dose and patient drug delivery rates when compared to the predicate, the Southmedic OxyMulti Mask.

T μ Q oNQ & &

December 2016 – Updated manufacture data from original report

References

Aerosol Research and Engineering Laboratories Inc. *Analytical Report for Certificate of Analysis and GLP Statement for project #10766.2*

Hui-Ling Lin, R D Restrepo, et al. *Effect of face mask design on inhaled mass of nebulized albuterol, using a pediatric breathing model*. Respiratory care, 2007

E. Saatci, D.M. Miller, et al. *Dynamic dead space in face masks used with noninvasive ventilators: a lung model study.* Eur Respir J 2004; 23; 129-135.

William C. Hinds. *Aerosol technology: Properties, Behavior, and Measurement of Airborn Particles*. John Wiley & Sons. 1999. pg 243.

Sanjay Sangwan MD, Burak K. Gurses MD, Gerald C. Smaldone MD, PhD *Facemasks and facial deposition of aerosols*. Pediatric Pulmonology. Volume 37, Issue 5, pages 447–452, May 20