In-Vitro Comparison of Six Continuous Nebulizers*

*S. David Piper, PE***

BACKGROUND: Continuous nebulization has become popular for treating patients with severe reversible airway disease. Continuous nebulization therapy has been shown to be safe, effective, and labor efficient as compared to other traditional medication aerosol treatments[1-11]. Although numerous studies have been done evaluating the clinically efficacy of continuous nebulization, little work has been done on comparing the various continuous nebulizers available. In this study, six continuous nebulizers, EZflow™, HEART®, MiniHEART™, UniHEART™, IVHEART™, and Hope™, are evaluated for medication delivered to patient and particle size. METHODS: Each nebulizer was set up and used as described on the product insert accompanying each nebulizer. Each nebulizer was mixed to provide 10 mg/hour of albuterol sulfate based on the nominal output of each nebulizer. Reservoirs were filled to their maximum volume or enough for five hours of nebulization, whichever was less. Airflow was set initially to the nominal airflow specification of the nebulizer and than adjusted incrementally, up or down, until the mean output of the nebulizer, as indicated on the graduations of the nebulizer reservoir, matched the nominal output listed for the nebulizer. Each nebulizer was connected to an aerosol mask as described in the product insert. An inhalation flow of 10 L/min was simulated; entrained air was humidified. A cascade impactor was used to sample aerosol every hour. Medication delivered and particle size were determined using a spectrophotometer operating at 279 nm. RESULTS: In spite of the fact that each nebulizer was mixed to provide the same amount of medication, there were significant differences in the quantity of medication delivered to the patient. The EZflow Continuous Nebulizer™ was shown to deliver significantly more medication than the others ($p < 0.01$). The UniHEART™ and IVHEART™ delivered the least amount of medication. The HEART® had an MMAD of 3.6 microns, which was significantly more than the other nebulizers which had particle sizes ranging from 2.0 to 2.5 microns ($p < 0.01$). CONCLUSION: Clinically important differences exist between different continuous nebulizers. When comparing the performance of nebulizers it is important to conduct testing under identical conditions which simulate actual clinical use.

Continuous Nebulizer Therapy (CNT) has been shown to be an effective means of treating severe reversible airway disease. Numerous studies comparing CNT to traditional medication aerosol treatments have shown that, for patients with severe reversible airway disease or impending respiratory failure, CNT is both more effective and labor efficient[1-11]. There exists a number of different nebulizers which may be used to deliver CNT. Two newer generation nebulizers have recently become available, The EZflow™ and the Hope™. Little work has been done comparing the performance of these various nebulizers. Quantity of medication delivered and aerosol particle size (MMAD) are both important factors in evaluating the performance of any aerosol device. Aerosol particles are well known for there size instability due to environmental and configuration parameters. Although most manufacturers report particle size for their particular product, the information reported is of little value without a description of the particle testing method used. For example, the EZflow Continuous Nebulizer™ was shown in this study to have an MMAD of 2.4 microns. When the same nebulizer was tested with the same equipment and under the same conditions but with entrained dry air instead of humidified air, the MMAD was found to be 2.0 microns. When comparing the particle size of two different nebulizers, it is therefore important to compare them under the same testing conditions. It is the purpose of the study to compare the performance of different continuous nebulizers under identical simulated clinical conditions.

Methods

Nebulizers Evaluated

Six different continuous nebulizers were evaluated (Table 1). All nebulizers were provided from saleable stock; none were prototypes or otherwise prepared specifically for this study, and all were used as supplied from the manufacturer. All nebulizers were set up and used as described by the manufacturer on the product insert. As described on the product inserts, the HEART®, IVHEART™, and Hope™, which are too big to connect directly to an aerosol mask, were connected using a six foot length of blue 22 mm corrugated tubing. The HEART® and IVHEART™ were fixed in place with a IV-Pole bracket designed by the manufacturer. The EZflow™ and UniHEART™ connected directly onto the aerosol mask, the MiniHEART™ connected directly onto an aerosol mask with the use of a 22 mm ID connector. The initial flowrate, nominal output, reservoir volume, and expected duration for each nebulizer is listed in table 1.

---

* From Piper Medical Products, March 9, 1999, West Sacramento, CA 95691 1-800-810-1116, www.pipermedical.com

** S. David Piper, PE is a registered professional engineer with the state of California, President of Piper Medical Products, and has been involved with the invention and development of continuous nebulizers since 1990.

Table 1. Nebulizer Specification Comparison Table

	Nebulizer Name	Nominal Flowrate (L/min)	Nominal Output (mL/hour)	Reservoir Fill Vol. (mL)	Nominal Max. Duration (hours)	Connect to Mask? (Yes/No)	Antispill? (Yes/No)
A	EZflow™	3	6	25	4.2	Yes	Yes
B	HEART®	10	30	240	8.0	No	No
C	MiniHEART™	2	8	30	3.8	Yes+	No
D	UniHEART™	4	9	10	1.1	Yes	Yes
E	IV-HEART™	10	25	100	4.0	No	Yes
F	Hope™	13	25	200	8.0	No	No

+MiniHEART™ requires a 22 mm connector to connect to an aerosol mask.

Evaluation of Medication Delivered and Particle Size

Each nebulizer was filled to its maximum reservoir volume or with sufficient liquid to provide nebulization for 5 hours, whichever was less. Normal saline was mixed with albuterol sulfate (Sigma; St Louis) to provide 10 mg/hour at the nominal output of each nebulizer. Nebulizers were run for four hours or until aerosol ceased being produced. Nebulizer flows were adjusted up or down every hour until the indicated output per the graduations on the side of the nebulizer jar matched the nominal output of the nebulizer. An inhalation flow of 10 L/min was simulated through the aerosol mask, entrained air was humidified. A 7 stage cascade impactor (In-Tox Products; Albuquerque, NM) was used to sample aerosol from the simulated inhalation flow. The cutoff size for the stages of the cascade impactor were 5.59, 4.48, 3.40, 2.02, 1.14, 0.43, and 0.29 microns. Particles smaller than 0.29 microns were caught with a membrane filter. The cascade impactor was configured to sample isokinetically and operated at a flowrate of 1.6 L/min. The amount of albuterol captured on each stage was determined using a spectrophotometer (Barnstead/Thermolyne, Dubuque, IA). Quantity of albuterol delivered to patient was determined by the amount captured by all stages of the cascade impactor and the ratio of the sampling flow to the simulated inhalation flow or nebulizer flow, whichever was greater. Particle size (MMAD) was determined using a best fit plotting of the spectrophotometer data onto logarithmic graph paper intended for the cascade impactor. Cascade impactor samples were taken at the beginning of testing and every subsequent hour. Nebulizers which did not last 4 hours had a final cascade impactor sample taken prior to the initiation of sputtering. Each nebulizer was sampled 5 times with the cascade impactor, except the UniHEART. The UniHEART, which produced aerosol for only 55 minutes, was sampled with the cascade impactor twice. Cascade impactor sampling results were averaged together for each nebulizer.

Spectrophotometric Analysis of Albuterol

Calibration was performed using a stock solution of albuterol (40 ug/mL) prepared from powdered drug (Sigma; St Louis) and a standard curve was constructed from serial dilutions (20, 10, 5, and 0.0 ug/mL). An absorbance peak was found at 279 nm and all absorbance measurements were made at this wavelength. The amount of drug in test solutions was determined from the standard curve which was verified before and after every measurement.

Statistical Analysis

Summary statistics are reported with mean$\pm$SE. Differences between groups were determined by single or double tailed analysis of variance as appropriate. Statistical significance was set at $p < 0.05$.

Results

Quantity of Medication Delivered

In spite of the fact that each nebulizer was mixed to deliver the same amount of medication, there were significant differences in the amount delivered. The quantity of medication delivered for each nebulizer is shown in figure 1. The EZflow Continuous Nebulizer™ delivered 9.1 ± 0.6 mg/hour of abuterol which was significantly more than each of the other nebulizers ($p < 0.01$). The UniHEART™ and IVHEART™ delivered 6.9 ± 0.5 and 7.1 ± 0.5 mg/hour respectively, which was significantly less than each of the other nebulizers ($p < 0.04$). In every case, the gravimetric expulsion rate was less than the output indicated by the graduations on the side of the nebulizer. This was most notable in the UniHEART™ which was found to have a gravimetric dead volume of 2.4 mL and least notable with the EZflow which was found to have a gravimetric dead volume of 0.71 mL. The HEART®, IVHEART™, and Hope™ all required the use of a six foot length of corrugated tubing to connect to the aerosol mask. There was rain out in the tubing in each case. The HEART® was observed to have more rainout than the other nebulizers.

Particle Size Evaluation

There was significant differences in the Mass Median Aerodynamic Diameter (MMAD) for the six nebulizers tested. Measured MMAD for the six nebulizers is shown in figure 2. The HEART® nebulizer had a MMAD of 3.6 ± 0.6 microns, which was significantly more than each of the other nebulizers ($p < 0.01$). The other nebulizers had MMAD's ranging from 2.0 to 2.5 microns.

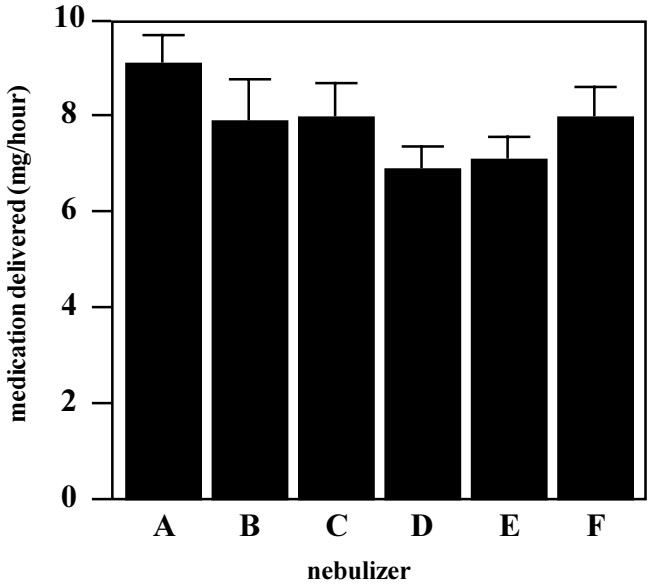

FIGURE 1. effect of nebulizer on amount of albuterol delivered to patient (mean and standard deviation).

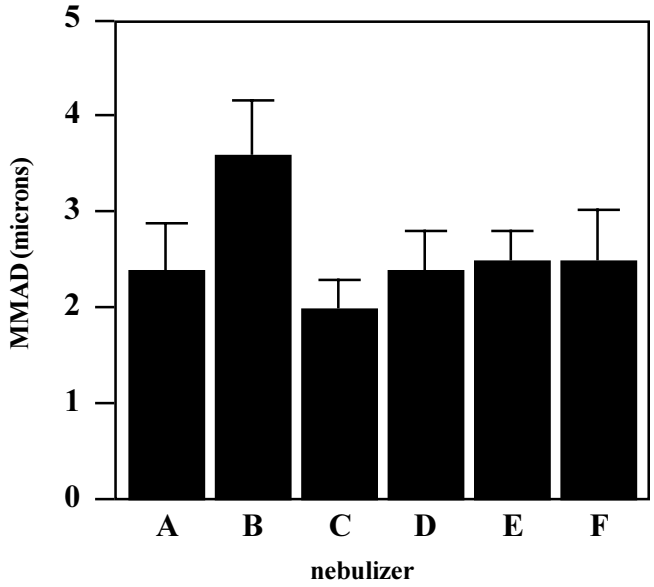

FIGURE 2. effect of nebulizer on particle size (mean and standard deviation).

Discussion

In this study, it has been demonstrated that the continuous nebulizer used can have a significant affect on the amount and quality of aerosol delivered to the patient. Most noteworthy is that six nebulizers, mixed to deliver the same amount of medication per hour, actually delivered significantly different amounts. There are a number of likely causes for this phenomena. Most obviously, three of the nebulizers required corrugated tubing to connect to the aerosol mask. In each case rain out inside the tubing was observed, which means less medication was delivered to the simulated patient. In another study by Raabe et al[12], the HEART® was shown to deposit approximately 10% of its gravimetric output within the corrugated tubing leading to the aerosol mask. This would help explain some of the observed differences. Secondarily, it was observed, that in each case, the gravimetric output was always less than the output observed by the graduations of the nebulizer. This would imply that significant volumes of liquid within the nebulizer are being drawn from the reservoir and being continually sprayed onto the internal surface areas of the nebulizer. Such an increase in wetted surface area would invariably increase evaporation, thus increasing the gravimetric output of the nebulizer without a corresponding increase in delivered medication. Presumably during this process, albuterol is being deposited on the internal surfaces of the nebulizer. This was most certainly an important factor in the poor performance of the UniHEART™ which was observed to have a dead volume 2.4 mL or 24% of its initial reservoir volume. The EZflow Continuous Nebulizer™, which had the highest observed medication delivery rate, was designed specfically to circumvent both of these issues.

The variance in medication delivery rate was smaller than expected. In previous work it was shown that the reservoir concentration of a continuous nebulizer can theoretically increase to as much as two times the initial concentration[12]. Ordinarily, medication delivery rate would also be expected to double at the end of treatment. That was not found to be the case in this study. Invariably, the cascade impactor sample taken at the end of treatment was found to be less than at least one of the other previous cascade impactor samples, and there was generally no upward trend in medication delivered during the course of treatment. Although the concentration of the nebulizer may go up, apparently the actual medication output does not. This issue deserves further study but is outside the scope of this paper.

With the exception of the HEART®, which was shown to have a larger particle size, there was no significant difference in particle size for the other nebulizers. An important objective of this study was to perform particle size testing under identical conditions which could be used as a fair comparison of the various continuous nebulizers. It is worth repeating that testing under different conditions will always produce variations in measured MMAD. Waldrep et al[13] in their evaluation of continuous-flow jet nebulizers aerosolizing beclomethasone dipropionate Liposome showed that the HEART had a MMAD of 7.2 microns, which is exactly twice the MMAD measured in this study. The difference might be explained, in part, by the nature of the fluid aerosolized in the Waldrep et al[13] study.

Raabe et al[12] also measured the particle size of the HEART and the MiniHEART at a flowrate of 10 and 2 L/min respectively and found the HEART to have an MMAD of 2.0 $\pm$ 0.9 microns and the MiniHEART to have an MMAD of 2.4 $\pm$ 0.7 microns. Although the MMAD measured for the MiniHEART is in good agreement with this study, the MMAD measured for the HEART is significantly less. Coincidentally, the MiniHEART was mixed to deliver 8 mg/hour of albuterol, which is similar to the 10 mg/hour used in this study, and the HEART was mixed to deliver 30 mg/hour, which was significantly different than the 10 mg/hour the HEART was mixed for

in this study. 30 mg/hour of albuterol sulfate is more medication than even the most severe patients generally receive. Furthermore, Raabe et al[12] did not measure concentrations of albuterol directly, as done in this study, but used a fluorescein trace and assumed that the proportion of concentration of albuterol to fluorescein remained constant. If albuterol does indeed deposit on the internal surfaces of the nebulizer, as suggested by the results of this study, then that assumption is in serious doubt. Lastly, Raabe et al[12] sampled aerosol with a cascade impactor running at 17 L/min while running the HEART at 10 L/min. There is no mention of where the additional 7 L/min came from or what state it was in. This could also play a significant role in explaining any discrepancies between the findings of Raabe et al[12] and the finding of this study.

Conclusions

Significant differences exist between the various continuous nebulizers available. The EZflow Continuous Nebulizer™ was shown to deliver more medication than the other continuous nebulizers tested. With the exception of the HEART® nebulizer, which had a large MMAD of 3.6 microns, all the other continous nebulizers had roughly equivalent particle sizes ranging from 2.0 to 2.5 microns. Further work should be done studying the delivery of medication to the patient over long periods of time with respect to the reservoir concentration of the nebulizer, and the impact of various clinically relevant environmental conditions and there affect on particle size. Differences in experimental design and environmental conditions can have a significant impact on measured particle size.

Product Sources

EZflow Continuous Nebulizer™, Piper Medical Products, West Sacramento, California, 1-800-810-1116, http://www.pipermedical.com

HEART®, MiniHEART™, UniHEART™, IVHEART™, Westmed, Tucson, Arizona

Hope™, B&B Medical Technologies, Sacramento, California

EZflow™ is a Trademark of Piper Medical Products

HEART® is a registered Trademark of Vortran Medical Technology, Inc.

MiniHEART™, UniHEART™, IVHEART™ are all Trademarks of Vortran Medical Technology, Inc.

Hope™ is a Trademark of B&B Medical Technologies

References

1. Portnoy J, Nadel G, Arnacio M, Wilsie Edger S. Continuous Nebulization for Status Asthmaticus. Annals of Allergy 1992 Jul; 69:1, 71-9.
2. Rudnitsky GS, Eberlein RS, Schoffstall JM, Mazur JE, Spivey WH. Comparison of Intermittent and Continuously Nebulized Albuterol for Treatment of Asthma in an Urban Embergency Department. Annals of Emergency Medicine, 1993 Dec, 22:12, 1842-6
3. Papo MC, Frank J, Thompson AE. A Prospective, Randomized Study of Continuous Versus Intermittent Nebulized Albuterol for Severe Status Asthmaticus in Children. Critical Care Medicine, 1993 Oct, 21:10, 1479-86
4. Shrestha M, Bidadi K, Gourlay S, Hayes J. Continuous vs Intermittent Albuterol at High and Low Doses in the Treatment of Severe Acute Asthma in Adults. Chest 1996 Jul, 110:1, 42-7
5. Buck ML, AACN Clin Issues, 1995 May, 6:2, 279-86
6. Craig VL, Bigos D, Britli RJ. Efficacy and Safety of Continuous Albuterol Nebulization in Children with Severe Status Asthmaticus. Pediatrics Emergency Care 1996 Feb, 12:1, 1-5
7. Montgomery VL, Eid NS. Low-Dose Beta-Agonist Continuous Nebulization Therapy for Status Asthmaticus in Children. J Asthma, 1994, 31:3, 201-7
8. Moler FW, Hurwitz ME, Custer JR. Improvement in Clinical Asthma Score and PaCO2 in Children with Severe Asthma treated with Continuously Nebulized Terbutaline. J Allergy Clin Immunol, 1998 Jun, 81:6, 1101-9
9. Khine H, Fuchs SM, Saville AL. Continuous vs Intermittent nebulized Albuterol for Emergency Management of Asthma. Academic Emergency Medicine, 1996 Nov, 3:11, 1019-24
10. Reisner C, Kotch A, Dworkin G. Continuous versus Frequent Intermittent Nebulization of Albuterol in Acute Asthma: A Randomized, Prospective Study. Annals Allergy Asthma Immunol. 1995 Jul, 75:1, 41-7
11. Olshaker J, Jerrard D, Barrish RA, Brandt G, Hooper F. The Efficiency and Safety of a Continuous Albuterol Protocol for the Treatment of Acute Adult Asthma Attacks. American Journal Emergency Medicine, 1993 Mar, 11:2, 131-3.
12. Raabe OG, Wong T, Wong G, Roxburgh J, Piper SD, Lee JIC. Continuous Nebulization Therapy for Asthma with Aerosols of Beta-Agonists. Annals Allergy Asthma Immunol. 1998 Jun, 80:6, 499-508
13. Waldrep JC, Keyhani K, Black M, Knight V. Operating Characteristics of 18 Different Continuous-Flow Jet Nebulizers with Beclomethasone Dipropionate Liposome Aerosol. Chest 1994 Jan, 105:1, 106-10