Particle size and airflow: Implications for nasal and paranasal sinus delivery

Summary: Topical intranasal drug delivery presents several challenges to the drug delivery system. These challenges include delivering a high concentration of drug throughout the nasal and paranasal sinus cavities while at the same time preventing delivery of the drug to the pulmonary system. Delivery systems include high volume nasal lavage, small particle nebulizers adapted from pulmonary delivery systems, spray bottles and metered dose inhalers (MDI). Each presents with its own issues. An alternative method of delivery is a large particle nebulizer delivering a sufficient airflow that generates a deep penetrating plume. This system is the NasoNeb® Nasal Nebulizer.

The NasoNeb Nasal Nebulizer is specifically designed for intranasal delivery of drugs. The NasoNeb System generates a unique plume that is characterized by large liquid particles delivered with sufficient airflow, which results in a deep, penetrating aerosol. This aerosol delivers a high percentage of medication into the nasal and paranasal sinus cavities while preventing unwanted pulmonary deposition observed with small particle delivery systems. Therapy delivered via the NasoNeb Nasal Nebulizer was shown to improve outcomes in a randomized, parallel, placebo-controlled trial.[7]

Particle Size Measurement of the NasoNeb Nasal Nebulizer

MedInvent contracted Powerscope, Inc. of Eden Prairie, MN to measure the particle size and velocity of the NasoNeb Nasal Nebulizer. Using an Artium Technologies Inc. Phase Doppler Interferometer (PDI® system), the team at Powerscope determined that the average particle size (mode) was 23.3 microns and that there were virtually no particles smaller than 15 microns.[18] The nasal cavity filters particles that are 10 microns and larger; thus, the nasal and paranasal sinus cavities are able to capture virtually all of the particles delivered via the NasoNeb Nasal Nebulizer that pass through the nasal valve.

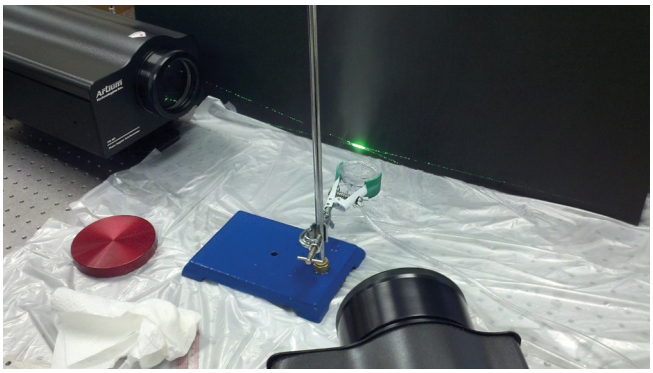

Table 1. Percentage of NasoNeb-generated particles by size, in microns[18]

Particle Size	NasoNeb System
<5 µm	0.0083±0.0098%
<10 µm	0.055±0.037%
>10 µm	99.94%±0.0468%

These data demonstrate the NasoNeb Nasal Nebulizer's ability to meet the requirements in the guidance established by the FDA with respect to developing intranasal drug delivery systems. These guidelines include the following:

> "When developing a drug product for nasal delivery, the aerodynamic characteristics of the formulation generated by the delivery system should be considered to ensure that the drug product will be retained in the nasal cavity and not inhaled into the lung. One important consideration is the aerodynamic-based sizing of the particles or droplets. Particles or droplets that are aerodynamically smaller than the standard 5 micron upper bound of the respirable fragment size can be inhaled. ***For nasal deposition, the optimal droplet or particle size should be, on the whole, substantially larger than the respirable fragment size."***[15]

Discussion

Unlike the NasoNeb Nasal Nebulizer, traditional jet and vibrating mesh nebulizers are specifically designed for delivery of medications to the lungs; as such, these devices generate respirable particles sized in the 3-5 micron range in order to reach the pulmonary mucosa. Therapy delivery to the lungs is typically offered with both oral (via mouthpiece attachment) and nasal (via mask attachment) routes.

When pulmonary devices are adapted for nasal delivery using nasal adapters, the particle size generated remains in the 3-5 micron range. In this size range, studies have demonstrated that 3% of the drug deposits in the nasal cavity, 18-22% deposits in the lungs, and the rest is lost to inhalation[8].

When the NasoNeb's large particles are coupled with the airflow generated by the NasoNeb compressor, they are distributed throughout the whole nasal cavity, including the clinically important superior and posterior structures, as demonstrated in two clinical trials[3,9]. Areas reached by the NasoNeb Nasal Nebulizer include the frontal recess/sinus, spheno-ethmoid recess, ethmoid cavity, sphenoid and maxillary sinuses, all turbinates, the middle meatus and olfactory cleft.

In the case of pulmonary drug delivery devices, airflow generated by the delivery system is considered counterproductive since particles driven at any velocity would be driven to the back of the throat, adhere to the mucosa, and not be available to the lungs. Therefore, excess air generated by the compressor is vented off and the respirable particles are held in a reservoir through which the patient inhales to deliver the medication. Small particle nebulizers adapted for nasal cavity therapy delivery also rely on patient inhalation for delivery; thus, particles from these systems are primarily delivered to the pulmonary system via the patient's breath[8]. Those particles that do deposit in the nasal cavity are concentrated in the nasal antrum and are carried through the floor of the nose to the throat by mucociliary clearance.[8] They have not been shown to reach the superior and posterior area of the nasal cavity with any appreciable level of concentration[8].

Pulmonary delivery of drugs dramatically increases the potential for systemic absorption and unwanted side effects. Intranasal drugs are eventually cleared by mucociliary clearance to the gut where they may be destroyed by the digestive action of the gut or metabolized to inactive moieties during first pass metabolism[10]. Drugs absorbed through the pulmonary mucosa bypass first pass metabolism and are thus systemically available[10]. For instance, fluticasone propionate has an oral bioavailability of <1% due to first pass metabolism yet has an absolute bioavailability (systemic+pulmonary) of 17% when delivered to the lungs via a DPI and 26 – 29% as a liquid delivered via an MDI[16].

Inadvertent delivery of topical drugs to the pulmonary system can lead to alteration of voice[13], antimicrobial resistance[12], eosinophilic pneumonia[13], chronic cough[13], and reduced lung function[10].

Spray bottles and Metered Dose Inhalers (MDI's) exhibit similar patterns, reaching only the first third of the inferior and middle turbinate at best[2]. These devices generate no airflow and as a result the particles lose significant momentum as soon as they are formed at the nozzle. The NasoNeb System, on the other hand, generates an air column that continues to propel the particles after they leave the device to help drive them deep into the nasal cavity.

The unique delivery characteristics of the NasoNeb System results in broad intranasal drug delivery with high intranasal drug retention.

Irrigation bottles are sometimes used off-label to deliver medication in a high volume of fluid (as much as 8 oz. are delivered in one dose). While irrigation bottles distribute liquid more broadly across the nasal mucosa, only 1.8% - 2.4% of the liquid is retained. The rest of the liquid washes out the contra-lateral nostril and down the sink, carrying virtually all of the medication into the environment[4,8]. The NasoNeb System delivers between 0.2 and15 ml total volume, ensuring that the medication stays in the nasal and paranasal sinus cavities and does not simply run down the sink. Repeat exposure to cold irrigation fluid has been linked to exostoses of the paranasal sinus cavities in the peer-reviewed literature.[1,5,11,14] Through its aerosolizing action, the NasoNeb System has been shown to warm refrigerated fluid by over 20° F.[6]

In the end, the clinical value of large particles supported by sufficient airflow may best be demonstrated by the positive outcomes observed in the treatment arm of a parallel, double-blinded, placebo controlled study of the response of perennial allergic rhinitis patients to Budesonide delivered via the NasoNeb Sytem compared to the same volume of saline delivered via the NasoNeb System. The investigators report a statistically-significant 50 LPM increase in Nasal Peak Inspiratory Flow in the treatment arm from baseline to endpoint ($p \leq 0.005$).[7]

Table 2. Comparing Intranasal Drug Delivery Systems

Intranasal Drug Delivery Options	Particle size	Supporting air flow	Intranasal deposition	Intranasal drug retention	Pulmonary deposition
NasoNeb Nasal Nebulizer	23.3 µm	Yes	Broad[3,9]	High	No
Small particle Nebulizers	3-5 µm	No	Antrum[8]	Low	Yes
Spray bottles	37-157 µm	No	Antrum[2]	High	No
Irrigation bottles	Fluid	No	Broad[4]	Low	No
Powered Irrigators[17]	10-15 µm	<1 lpm	Antrum	Low	No

Conclusion

Particle size is critical to ensure that the intranasal drug delivery deposits in the nasal and paranasal cavities. An appropriate level of airflow during delivery is critical to ensure that the particles are propelled past the nasal valve and reach the posterior and superior regions of the nasal cavity. Small particle nebulizers generate respirable particles in the 3-5 micron range that can be inhaled into the lungs, regardless of whether the user chooses an oral or nasal method of introduction. For nasal deposition, the optimal droplet or particle size should be, on the whole, substantially larger than the respirable fragment size, or larger than 5 microns[15].

The NasoNeb Nasal Nebulizer delivers a large particle, deep-penetrating aerosol that is captured by and deposited throughout the nasal and paranasal sinus cavities[3,9]. The NasoNeb System delivers a high concentration of drug to the target site while avoiding pulmonary deposition and the associated risk of unwanted side effects[9]. The NasoNeb System delivers a relatively small volume of liquid that stays in the nasal and paranasal sinus cavities, reduces waste associated with other therapy delivery options and is supported by clinical data[3,6,7,9].

References

1. Adelson, RT, Kennedy DW: "Paranasal sinus exostoses: possible correlation with cold temperature nasal irrigation after endoscopic sinus surgery" *The Laryngoscope* 2013, Jan: 123(1): 24 – 7
2. Mow Yee Foo, Yung-Sung Cheng, Ph.D., Wei-Chung Su, Ph.D., Maureen D. Donovan, Ph.D.: "The Influence of Spray Pattern on Intranasal Deposition" *J. Aerosol Therapy*, 2007:20:4: 495-508
3. Yuri M. Gelfand, MD; Samer Fakhri, MD; Amber Luong, MD, PhD; Seth J. Isaacs, MD & Martin J. Citardi, MD: "A Comparative Study of the Distribution of Normal Saline Delivered by Large Particle Nebulizer vs. Large Volume/Low Pressure Squeeze Bottle" 56th Annual Meeting of the American Rhinologic Society, September 25, 2010, page 38
4. Harvey, RJ, Denath, N, Srubiski, A, et. al: "Fluid residuals and drug exposure in nasal irrigation" *Otolaryngol. Head and Neck Surg*. 2009: 141:757-761
5. Haffey, MD, Timothy; Woodard, MD, Troy, Sindwani, MD, Raj:"Paranasal Sinus Exostoses: An Unusual Complication of Topical Drug Delivery Using Cold Nasal Irrigations" *The Laryngoscope* 2012, Sep;122(9):1893-7
6. Holmes, MD, Janalee; Haffey, MD, Timothy; Woodard, MD, Troy, Sindwani, MD, Raj: "Ambient Warming of Nasal Irrigation Solutions: Implications for Safe Topical Drug Delivery and Patient Compliance"; COSM 2013 program, p 42
7. Kristal Brown MD, James Lane BSc, Marianella Paz Silva, MD, Marcy DeTineo BSN, Robert M. Naclerio MD, and Fuad M. Baroody, MD: "Effects of Intranasal Budesonide Delivered by Nasal Nebulizer on Symptoms and Objective Measures of Nasal Congestion in Perennial Allergic Rhinitis" *Int Forum of Allergy Rhinol* 2014; 4:43-48
8. Laube, Ph.D., Beth: "Devices for Aerosol Delivery to Treat Sinusitis" J. Aerosol Therapy, 2007:7:Supplement 1:S1-S18
9. Manes RP, Tong L, Batra PS.: "Prospective evaluation of aerosol delivery by a powered nasal nebulizer in the cadaver model" *Int Forum Allergy Rhinol*, 2011; 1:366–371
10. Molina, MD, Pablo E.; Anzueto, MD, Antonio; Aoki, MD, Teresa; Restrepo, MD, Marcos: "Drug –Induced Acute Eosinophilic Pneumonia Induced by Inhaled Vancomycin" CHEST October 2004; 236 (4 Meeting Abstracts) 993S-993S.
11. Ramakrishnan, MD, Jeevan B.; Pirron, MD, Jose A.; Perepletchikov, MD, PhD; Ferguson, MD FAAOA, Berrylin J.: "Exostoses of the paranasal sinuses" *The Laryngoscope* 2010 Dec: 120(12) 2532 - 2534
12. Rubin BK. Aerosolized antibiotics for non-cystic fibrosis bronchiectasis. *J Aerosol Med Pulm Drug Deliv* 2008;21(1):71-6.
13. Santos, Roberto P; Awa, Emad; and Anbar; Ran D: "Inhaled tobramycin solution-associated recurrent eosinophilia and severe persistent bronchospasm in a patient with cystic fibrosis: a case report" BMC Pediatr. 2007; 7: 11.
14. Schwarts, KM, Eckel, LJ; Black, DF; Lehman, VT; Diehn, FE; Hunt, CH; Lindell, EP: "Irrigation Nose: CT Findings of Paranasal Exostoses" Open Neuroimag. J. 2012; 6:90-91
15. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER): "Guidance for Industry Sinusitis: Designing Clinical Development Programs of Nonantimicrobial Drugs for Treatment" November 2006.
16. Winkler, Julia; Hochhaus,Guenther; Derendorf , Hartmut: "How the Lung Handles Drugs: Pharmacokinetics and Pharmacodynamics of Inhaled Corticosteroids" *Proc Am Thorac Soc* December 1, 2004 vol. 1 no. 4 356-363.
17. "Performance Analysis: The NasaTouch™ NT7001 Powered Nasal Irrigator", MedInvent, LLC
18. "Particle Size and Airflow: Implications for nasal and paranasal sinus delivery," White Paper, MedInvent, LLC