Comparison of Nasal Deposition and Clearance of Aerosol Generated by a Nebulizer and an Aqueous Spray Pump

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INTRODUCTION

The nasal cavity has a large surface area (150 cm^2) available for drug targeting (1). Gamma scintigraphy has been used as a tool to evaluate nasal deposition of radiolabeled aerosol emitted from pressurized MDIs (2), nasal drops (3), and aqueous spray pumps (4). The method most commonly used to deliver medications to the nasal cavity is the aqueous spray pump. Studies investigating the *in vivo* deposition pattern of droplets administered by a spray pump indicate that local distribution is primarily in the anterior portion of the nasal cavity (3,5). Thus, the spray pump does not take full advantage of the entire surface area leaving large portions of the nasal cavity unexposed to drug.

To cover greater surface area, a nasal aerosol delivery system should generate small, slow moving particles to minimize inertial impaction in the anterior nasal cavity. A nebulizer could potentially fulfill these criteria. Since nebulizers are traditionally used to target the lung via the oral cavity, we modified a nebulizer system to direct aerosol into the nasal cavity. To investigate this prototype "nasal" nebulizer, we conducted a study comparing nasal deposition patterns from a typical aqueous spray pump and nasal nebulizer in a group of healthy volunteers. Mucociliary clearance was investigated since it is a pathway for potentially removing drug from the nasal cavity. The study also assessed lung deposition and particle size of the aerosol emitted from the nasal nebulizer and spray pump.

MATERIALS AND METHODS

Study Protocol

The study was a randomized trial consisting of two visits. On one visit, volunteers inhaled ^{99m}technetium (^{99m}Tc) radiolabeled saline aerosol into the nasal cavity from a nebulizer fitted with a nose-only adapter. On another visit, volunteers inhaled an analogous solution from a spray pump. After inhalation of the aerosol, each volunteer underwent gamma camera imaging of the nasal cavity over a 30 minute period. Images were analyzed for initial deposition pattern and for the removal of the radiolabel by mucociliary clearance over 30 minutes. Each volunteer's nasal cavity was also imaged during inhalation of ^{133}xenon (^{133}Xe) gas.

Study Population

Seven healthy volunteers and one mildly asthmatic volunteer, between the ages of 20 and 50, were recruited for this study (5 females and 3 males). The asthmatic volunteer was symptom free and taking no medication throughout the study. Informed consent was obtained from each volunteer and research was conducted under the tenets of the Declaration of Helsinki. This study was approved by the Johns Hopkins University Institutional Review Board.

Materials

The aerosol solution consisted of normal buffered saline admixed with ^{99m}Tc pertechnetate (Syncor Inc., Baltimore, MD) complexed with diethylene triamine pentaacetic acid (DTPA) (Syncor Inc., Baltimore, MD) to reduce the rate of disappearance by systemic absorption.[4] The average radiation dose of ^{99m}Tc was 19 μCi. Volunteers were also exposed to approximately 10 mCi of ^{133}Xe gas (Syncor, Inc., Baltimore, MD) during acquisition of a xenon ventilation image. Doses of ^{99m}Tc and ^{133}Xe were quantified using a dose calibrator (Capintec, Inc., Ramsey, NJ).

Administration of Xenon Gas

Volunteers inhaled ^{133}Xe gas through their nose from a Pulmonex Xenon System (Biodex Medical Systems, Shirley, NY), while their right nostril was positioned adjacent to a large field of view gamma camera (GE Maxicamera 400, St. Albans, Hertfordshire, England). This procedure is detailed in Suman, *et al.* (7). The outline of the each volunteer's nasal cavity was delineated from the xenon ventilation scan. This nasal outline was then superimposed on the registered images from the spray pump and nebulizer for each subject to provide a functional border for deposition analysis.

Administration of Radioaerosol by Nasal Spray Pump

A quantity of 6 ml of radiolabeled saline were added to an empty Beconase AQ® nasal spray pump (Allen & Hansburys, Research Triangle Park, NC). The spray pump was primed

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[4] In healthy nonsmoking adults, the total counts from a ^{99m}Tc DTPA aerosol delivered to the lungs decreases by 16 ± 8% in 20 minutes compared to no change in total counts from a nondiffusible ^{99m}Tc sulfur colloid aerosol (6). We concluded that approximately 20% of the ^{99m}Tc DTPA was systemically absorbed from the lung in 20 minutes. We chose ^{99m}Tc DTPA over ^{99m}Tc sulfur colloid since the former demonstrated radiation dose reproducibility, while the latter exhibited erratic dosing due to a binding of sulfur colloid to the nebulizer cup. References discussing nasal absorption of DTPA versus sulfur colloid, were not found.

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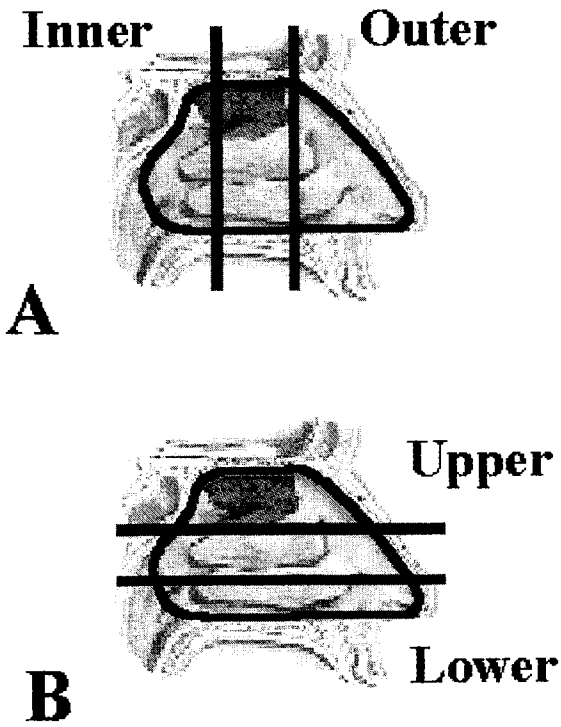

Fig. 1. Schematic of nasal deposition analysis with borders delineated from the ventilation scan and regions of interest. Inner and outer zones represent the anterior and posterior regions of the nasal cavity respectively (A). The upper zone depicts the superior areas, which include the olfactory region, and the lower zone denotes the floor of the nasal cavity and inferior turbinate (B). The blue area represents the olfactory region.

according to the manufacturer's instructions. Volunteers were instructed to lean their head slightly forward while keeping the pump upright, then inhale a single spray into each nostril with the opposing nostril closed and exhale through the mouth.

Administration of Radioaerosol by Nasal Nebulizer

A quantity of 1.4 ml of radiolabeled saline was added to a Hudson T Up-Draft II nebulizer cup (Hudson RCI, Irvine, CA) fitted with a nasal adapter specifically designed to simultaneously administer aerosol into both nostrils without depositing activity on the outside of the nose. The nebulizer was supplied with 20 psig compressed air. A dosimeter (Rosenthal-French, Baltimore, MD) regulated each compressed air pulse at 1.1 seconds during nebulization. After manually initiating nebulization, volunteers were instructed to inhale with a slow, shallow inspiration through the nose and exhale through the mouth.

Aerosol Scintigraphy Images

Immediately after inhalation of radioaerosol, each volunteer was positioned with his or her right nostril flush against the gamma camera to acquire a lateral image of deposition in the nasal cavity. Additional images were obtained at 15 and 30 minutes to quantify losses primarily due to mucociliary clearance, and to a lesser extent to systemic absorption. Images were stored on computer for subsequent processing (SMV, Twinsburg, OH).

Nasal Deposition Analysis

Regional deposition of ^{99m}Tc in the nose was quantified in terms of an inner versus outer zone, and upper versus lower

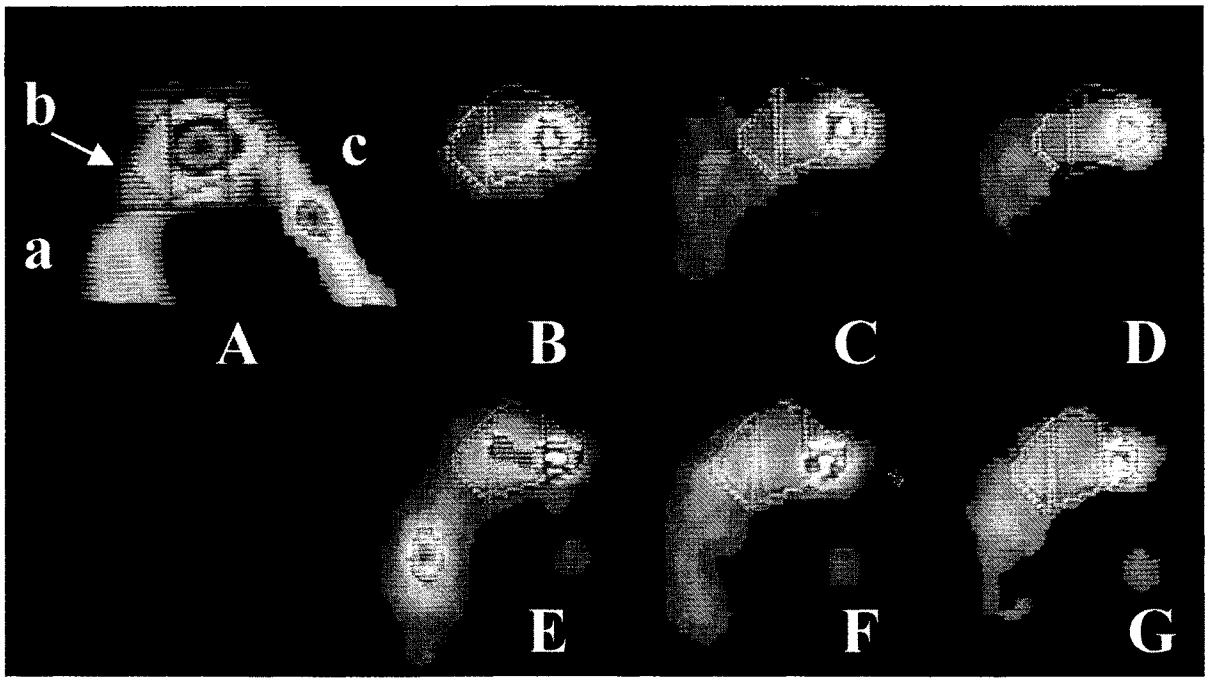

Fig. 2. Lateral xenon image defining the outline of the nasal cavity of a typical volunteer (A). This image also depicts the pharynx (a), the nasopharynx (b) and the tubing connecting the nasal adapter to the Pulmonex Xenon System (c). Aerosol images are shown at 0, 15, and 30 minutes for the aqueous spray pump (B-D) and nasal nebulizer (E-G). White indicates areas with the highest radioactivity while black indicates no radioactivity is present.

zone (Fig. 1). The inner zone represented the posterior third of the nasal cavity as delineated from the xenon ventilation scan. The outer zone represented the anterior third of the nasal cavity, beginning at the nostril and containing most, if not all, of the non-ciliated epithelium. The upper zone represented the part of the nasal cavity containing the superior turbinate and olfactory region, while the lower zone represented the floor of the nasal cavity and inferior turbinate. Counts per picture element (pixel) per minute were calculated for each zone in the radioaerosol images. Inner:outer (I:O) and upper:lower (U:L) ratios were derived from these calculations.

Mucociliary Clearance Analysis

Summing the radioactivity (counts per minute, cpm) of droplets depositing in the inner, middle and outer zones of the nasal image gave an estimate of deposition in the entire nasal cavity. Clearance of the radiolabel by mucociliary mechanisms was calculated as the percent change in cpm from time 0 to 15 and 30 minutes. Cpm at 15 and 30 minutes were decay corrected to time 0.

Lung Deposition Analysis

Two volunteers also underwent imaging of their posterior lungs after the initial nasal image. The amount of radioactivity (cpm) deposited in the lungs and nose was converted to μCi using the method described by Macy and Marshall (8). Radioactivity of droplets deposited in the nasal cavity was decay corrected to the time of the lung image. Lung deposition was calculated as a percent of the total amount of radioactivity deposited in the lungs and nose.

Particle Size Analysis

Particle size for the nasal nebulizer and spray pump was determined using a Malvern Mastersizer (Malvern Instruments, Ltd., Malvern, UK). The nebulizer and spray pump were positioned 2.5 cm below the laser beam and 3.5 cm from the receiver. A 300 mm lens was used. A quantity of 6 ml and 1.4 ml of saline mixed with DTPA were added to the spray pump and nebulizer, respectively. The spray pump and nebulizer were actuated by the same methods as described above for *in vivo* administration. Particle size is reported as the mean volume diameter (D_{V50}) for each delivery system (n = 3).

Data Analysis

All group data are presented as mean ± standard deviation. Statistical analyses comparing the regional deposition (I:O and U:L ratios) and percent clearance at 15 and 30 minutes for the nebulizer versus the spray pump were performed using the Wilcoxon-signed rank test. A Spearman rank-correlation was performed to investigate possible relationships between individual I:O and U:L ratios with the two delivery devices. P-values less than 0.05 were judged to represent significant differences.

RESULTS

The borders of the nasal cavity, as defined by the xenon ventilation scan (Fig. 2A), were superimposed on each volunteer's scintigraph. These borders provided an indication of the available surface where aerosol could deposit. The deposition and subsequent clearance of aerosol from the nebulizer and spray pump in a typical volunteer is shown in the other frames of Fig. 2. Initial deposition with the spray pump (2B) indicated that the radioactive droplets primarily deposited anteriorly as indicated by the "hot spot" in the front of the nose. Black areas in the scintigraph indicated no deposition in the upper nasal cavity. At 15 minutes, 39% of the deposited droplets were cleared primarily from the posterior regions into the nasopharynx (2C). At the 30 minutes, 42% of the deposited droplets were cleared from the spray pump image (2D). In contrast, initial deposition with the nebulizer showed that droplets were distributed to all regions of the nasal cavity (2E). A "hot spot" of radioactive droplets was present with the nebulizer, but was less intense than the spray pump. This meant that more aerosol distributed further back into the nasal cavity. There was also deposition in the pharynx and on the lips of the volunteer. At 15 minutes, 26% of the deposited droplets were cleared from the nasal cavity. The pattern of clearance was similar to the spray pump with the exception that activity was still present in the upper region (2F). At 30 minutes, 34% of the deposited droplets were cleared from the nebulizer image (2G). Since the addition of DTPA only slowed absorption of the radiolabel rather than preventing it, mucociliary clearance was not investigated beyond 30 minutes.

The analysis of regional aerosol deposition within the nasal cavity is shown in Table 1. Mean I:O ratios were significantly higher for the nebulizer, averaging 0.211 ± 0.153, compared to the spray pump which averaged 0.073 ± 0.068 ($p < 0.04$). The higher I:O ratio indicated that deposition in the posterior region of the nasal cavity was enhanced with the nebulizer. Mean U:L ratios were significantly higher with the nebulizer, averaging 0.517 ± 0.340, compared to the spray pump which averaged 0.331 ± 0.135 ($p < 0.01$). These results indicated that the nebulizer deposited more aerosol in the upper portion of the nasal cavity.

A Spearman rank-correlation test demonstrated that there was a significant correlation between U:L ratios obtained with the nebulizer and spray pump ($p < 0.01$). For example, volunteer 8 had the largest U:L ratio for both the nebulizer and spray pump. This suggests that anatomical factors may play a key role in determining which individuals achieve greater deposition in the superior regions of the nasal cavity. There was no significant correlation with respect to I:O ratios obtained from with the nebulizer and spray pump.

Table I. Regional Analysis of Deposition Pattern

Volunteer	Neublizer I:O	Spray pump I:O	Neublizer U:L	Spray pump U:L
1	0.184	0.028	0.200	0.151
2	0.113	0.108	0.692	0.307
3	0.412	0.029	0.382	0.353
4	0.161	0.032	0.372	0.229
5	0.475	0.148	0.604	0.454
6	0.203	0.031	0.413	0.396
7	0.073	0.011	0.223	0.207
8	0.065	0.194	1.248	0.553
Mean	**0.211**	**0.073**	**0.517**	**0.331**
SD	**0.153**	**0.068**	**0.340**	**0.135**

Clearance at 15 and 30 minutes for the two delivery systems are presented in Fig. 3. Clearance at 15 minutes averaged 19.0 ± 10.9% for the nebulizer and 27.1 ± 8.6% for the spray pump. Percent clearance at 30 minutes averaged 28.2 ± 12.5% and 34.1 ± 7.6% for the nebulizer and spray pump respectively. There were no significant differences between the two delivery systems at either time interval at the 0.05 level.

Percent deposition of the aerosol within the lungs of the two volunteers with the nebulizer was 33.3% and 58.0%, respectively. There was no lung deposition when the same volunteers used the nasal spray pump.

The D_{v50} for the nebulizer was 6.0 μm whereas the D_{v50} for the spray pump was 79.3 μm.

DISCUSSION

Nasal Deposition Analysis

Results from the deposition study in the eight volunteers indicated that the nasal nebulizer significantly increased deposition beyond the anterior nasal cavity. The spray pump deposited droplets primarily in the anterior portion of the nasal cavity. Anterior deposition of droplets is the combined result of the nasal anatomy and droplet size (9). As droplets enter the nose, they pass through the nasal vestibule, which is associated with turbulent, high velocity airflow (10). The inferior turbinate is located at the junction of the nasal vestibule and the posterior 2/3 of the nasal cavity. It is likely that the inferior turbinate acted as a baffle such that the larger droplets produced by the spray pump, deposited by inertial impaction. Droplets generated by the nebulizer deposited in more superior and posterior regions of the nasal compared to the spray pump. The nebulizer minimized impaction in the anterior region by producing smaller droplets.

Mucociliary Clearance Analysis

After drug deposits in the nose, it can be absorbed into the blood supply, be mechanically eliminated by blowing or wiping of the nose, or be removed from the nasal cavity by mucociliary clearance. In healthy humans, a particle that deposits in the nose is swept to the back of the nasal cavity by cilia and swallowed in an average of 15 minutes (11). Mucociliary clearance, therefore, may prevent drugs from maintaining contact with the nasal epithelium. Previous studies have shown that drugs, which deposit in posterior regions of the nasal cavity, are cleared faster and absorbed to a lesser extent (12). This is because the cilia that are responsible for clearance are primarily located in the posterior 2/3 of the nasal cavity (13). Therefore, one might expect that drugs deposited in these regions to be cleared too rapidly for optimal absorption despite coverage of more surface area. In fact, we found no significant differences between the numerical values for mucociliary clearance for the nebulizer and spray pump at 15 and 30 minutes. However, 7 of 8 volunteers showed slower clearance of the radiolabel with the nebulizer. One explanation for the observed slower clearance in those individuals could be that the nebulizer deposited aerosol in the upper portions of the nasal cavity including the olfactory region. Cilia located in these areas are less densely distributed than in regions along the floor of the nasal cavity (14). Thus, droplets that deposit in upper regions of the nose may be retained for a longer period of time than those on the floor of the nasal cavity.

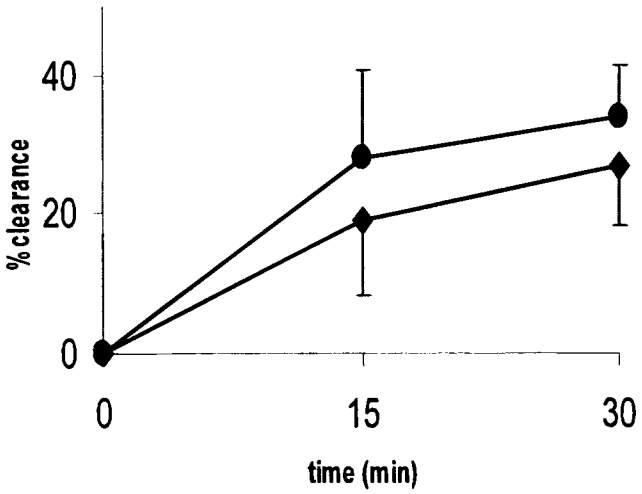

Fig. 3. Removal of radiolabel from the nasal cavity primarily attributed to mucociliary clearance from the nasal nebulizer (♦) versus the aqueous spray pump (●) at 0, 15 and 30 minutes. The symbols represent mean ± SD.

Lung Deposition and Particle Size Analysis

As expected, there was considerable lung deposition with the nasal nebulizer in the two volunteers who were studied. This is a result of the size of the particles produced by the nebulizer. Particles in the range of 2–10 microns deposit in the nose (9), but a large fraction by-pass it entirely and deposit in the lungs. In some cases, lung plus nasal deposition could be beneficial by targeting both organs with one delivery system. However, the choice of excipients that can be safely delivered to the lungs is limited. Therefore, the toxicological implications, as well as the regulatory issues associated with use of pulmonary excipients, should be considered before attempting simultaneous delivery of aerosol to the nose and lungs. A system that generates particles with an aerodynamic size between 10–20 μm (9), would be expected to minimize lung deposition, while preserving the advantages noted above. This laboratory is pursuing such a system.

CONCLUSIONS

This study demonstrated that a nebulizer that is adapted to deliver aerosol into the nose can deposit droplets in areas that a spray pump cannot reach. Although the nebulizer covered greater surface area with aerosol, retention of the aerosol was similar to that observed with the spray pump. This was probably because the increased coverage was in regions of the nose where cilia is less densely distributed leading to slower rate of mucociliary clearance.

Extended coverage to all surfaces of the nasal epithelium by a drug could maximize topical exposure or increase absorption. The efficacy of local or systemically acting agents could be facilitated by this deposition pattern. Increased nasal exposure to drug could also decrease the need for absorption promoters, which are often irritating to the nasal surface. Future research will investigate if targeting such nasal surfaces with

a nebulizer translates to improved drug absorption and clinical benefits.

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