

# NASAL NEBULIZERS VERSUS AQUEOUS NASAL SPRAY PUMPS: A COMPARISON OF DEPOSITION PATTERNS IN HUMAN VOLUNTEERS

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## SUMMARY

The purpose of this study was to test the hypothesis that the distribution of nasally administered aerosol within the nasal cavity could be enhanced by delivery of aerosols from nebulizers rather than aqueous spray pumps. The nasal deposition of a <sup>99m</sup>Tc radiolabeled saline solution administered by nebulizer or aqueous spray pump in 6 human volunteers was quantified by gamma scintigraphy. Deposition was expressed in terms of ratios that represented inner versus outer, and upper versus lower, zones of the nasal cavity. <sup>133</sup>Xenon gas was used to delineate the nasal cavity. Results indicated that aerosol deposition in the posterior and superior regions of the nasal cavity was significantly enhanced using nebulization compared to the spray pumps.

## INTRODUCTION

A function of the nasal cavity is to filter airborne particles from the inhaled airstream, thereby sparing the lower airways potentially harmful exposure to airborne contaminants. It is believed that most particles >10µm are retained in the nose, while the fate of those <10µm is less certain (1). This filtering role affects deposition of therapeutic aerosol particles inhaled through the nose. Understanding the major factors that influence nasal deposition is essential for optimizing delivery of therapeutic agents into the nasal cavity for local or systemic activity.

One important factor that determines where particles deposit in the nasal cavity is the delivery system itself (2). For example, nasal drops have been shown to cover a greater surface area in the nose compared to an aqueous spray pump (3). However, administering drops is not a practical method of drug delivery for many patients. Aqueous spray pumps have been demonstrated to deposit particles primarily in the anterior portion of the nose (3) which leaves a significant area of the nasal cavity unexposed to drug. Both of these systems cause solution to drip out of the nose. Pressurized nasal MDIs overcome dripping but deposit particles in a more localized manner in the anterior portion of the nose compared to aqueous pumps (4). Stinging sensations and the

switch to environmentally acceptable propellants, have reduced interest in this mode of delivery. These factors suggest that traditional delivery methods may not be optimal for drug delivery to the nose.

Aqueous nasal spray pumps and pressurized MDIs tend to deposit particles in the anterior portion of the nasal cavity by inertial impaction. This probably is due to the large particle size of the spray droplets (30-60  $\mu\text{m}$ ) from aqueous pumps (5) and the rapid exit velocity of particles from pressurized inhalers. Smaller droplets are difficult to produce using existing aqueous spray pump technology because patients are not capable of generating the forces (between their thumb and fingers) needed for pumps to produce finer particle size distributions. Two-phase mechanical spray pumps (which simultaneously compress air and drug solution) can produce substantial numbers of droplets smaller than 30  $\mu\text{m}$  (6) at attainable pressures. However, the fraction of smaller droplets remains low and their commercial utility is unproven. Small, slow moving droplets can be produced by nebulization and inhaled via a nose-only adaptor. Theoretically, such particles should minimize immediate nasal impaction, thereby increasing the likelihood of deposition beyond the anterior portion of the nose. The purpose of this study was to test the hypothesis that the distribution of particles within the nasal cavity could be enhanced by delivery of aerosols by nebulizers rather than aqueous spray pumps.

## METHODS

**Study Population:** Five normal (3 female and 2 male), and one mildly asthmatic male volunteer, between the ages of 20 and 50, were recruited for this study. The asthmatic volunteer was symptom free and taking no medication throughout the study. One normal volunteer noted having nasal drainage on one day of the study.

**Study Design:** This was a randomized trial consisting of two visits. On one visit, volunteers inhaled radiolabeled saline aerosol into the nasal cavity from a nebulizer and nose-only adaptor. On the other visit, volunteers inhaled an analogous solution from an aqueous spray pump. After inhalation, the head of each volunteer was imaged with a large field of view gamma camera (GE Maxicamera 400, St. Albans, Hertfordshire, England) equipped with an all-purpose parallel hole collimator. On one visit, a ventilation image of each volunteer's nasal cavity was acquired during inhalation of  $^{133}\text{Xe}$  gas.

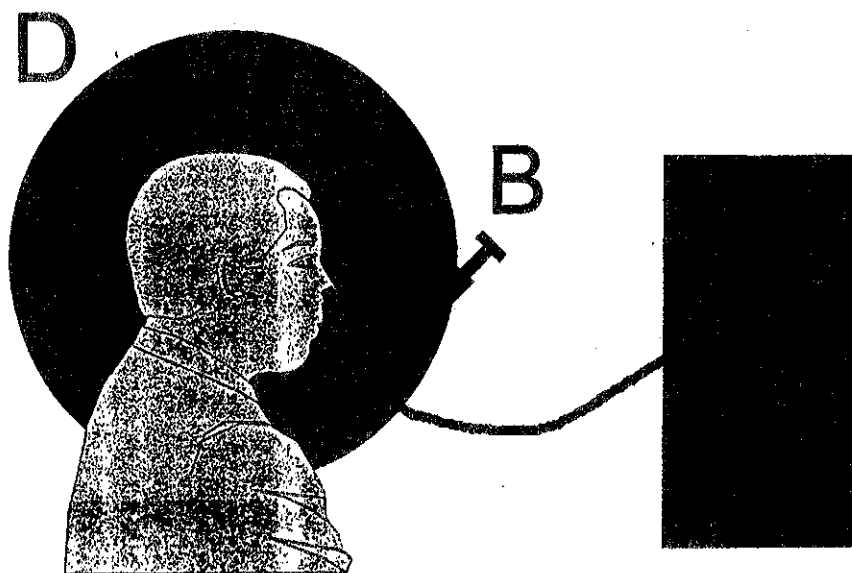
**Materials:** The aerosolized solution consisted of normal buffered saline admixed with  $^{99\text{m}}\text{Tc}$ -pertechnetate (Syncor Inc., Baltimore, MD) complexed with diethylene triamine pentaacetic acid (DTPA) to reduce the rate of disappearance by systemic absorption. The average radiation dose for each volunteer was 19  $\mu\text{Ci}$  from either the nasal spray pump or nebulizer. 10 mCi of  $^{133}\text{Xe}$  gas (Syncor, Inc., Baltimore, MD) was administered to acquire the ventilation image. The amount of radioactive  $^{99\text{m}}\text{Tc}$  and  $^{133}\text{Xe}$  filled into the spray pump or nebulizer was quantified using a radioisotope dose calibrator (Capintec, Inc., Ramsey, NJ).

**Administration of Radioaerosol by Nasal Spray Pump:** Six ml of radiolabeled saline was added to an empty Beconase AQ<sup>®</sup> nasal spray pump (Allen and Hansburys, Research Triangle Park, NC). The spray pump was primed four times according to the manufacturer's instructions. Following training in appropriate technique, each standing volunteer inhaled a single spray into each nostril. Volunteers were instructed to place the spray tip into each nostril while keeping the bottle perpendicular to the ground, and to actuate the pump while initiating a gentle inhalation through the nose with their mouth closed.

**Administration of Radioaerosol by Nebulizer:** 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 adaptor specially designed to simultaneously administer aerosol into both nostrils (Figure 1). The nebulizer was supplied with 20 psig compressed air for 1.1 seconds using a dosimeter (Rosenthal-French, Baltimore, MD). No make-up air was allowed to enter the adaptor. After manually initiating airflow, standing volunteers were instructed to inhale gently throughout the nebulization period while keeping the unit perpendicular.



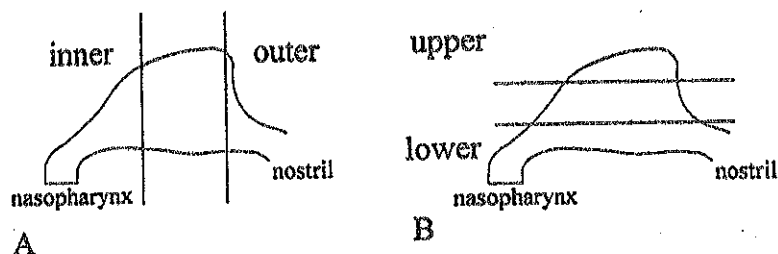
**Figure 1.** Prototype of the nasal adaptor, Hudson T Up-Draft II nebulizer and dosimeter used to administer the nebulized aerosol.



**Figure 2.** Schematic of the xenon system (A) which supplies air to the volunteer and prevents injected xenon (B) from escaping into the room. A nasal adaptor directs gas into the nasal cavity (C). The volunteer is positioned with their right nostril adjacent to the gamma camera head (D) for imaging.

**Aerosol Scintigraphy Images:** Immediately after inhalation of radioaerosol, each volunteer was positioned with their right nostril flush against the gamma camera to acquire a lateral image of the nasal cavity. Acquisition lasted 4 minutes for 5 volunteers and 3 minutes for one volunteer. The computerized images were stored for subsequent processing (SMV, Twinsburg, OH).

**Administration of Xenon Gas:** Volunteers inhaled  $^{133}\text{Xe}$  gas through their nose from a Pulmonex Xenon System (Biodex Medical Systems, Shirley, NY). Their right nostril was positioned adjacent to the gamma camera (Figure 2). Following bolus injection of xenon into the inhaled air-stream an image was acquired for 10 seconds while the volunteer held their breath. This duration was designed to allow the gas to diffuse into all regions of the nasal cavity. The volunteer then



**Figure 3.** Lateral view of defined region of interest. 3A shows the inner and outer zones of the nasal cavity while 3B depicts the upper and lower zones.

began breathing through the nose to allow equilibration of the gas throughout the respiratory tract. One minute after injection a second image was acquired for 1 minute. Regions of interest were defined on the ventilation scan that gave the most distinct outline of the nasal cavity in each volunteer.

**Regional Analysis:** Regional  $^{99m}\text{Tc}$  deposition was quantified in the inner versus outer zone, and upper versus lower zone of the nasal image (Figure 3A and 3B respectively). These regions of interest were first delineated on the ventilation image. The ventilation image was divided into three vertical regions using proprietary software. Similarly, the height of the ventilation image was divided into three horizontal regions. During automated computer processing, the radioaerosol images from the spray pump and nebulizer were each registered with the ventilation image. The regions delineated on the ventilation scan were then superimposed on the two previously registered radioaerosol images. This allowed the inner and outer zones as well as the upper and lower zones to be standardized on all three images. Counts per picture element (pixel) per time were calculated for each zone (inner, upper, outer or lower) in the two radioaerosol images. Inner:outer (I:O) and upper:lower (U:L) ratios were derived from these calculations.

The inner zone represented the posterior third of the nasal cavity as delineated by the 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. A higher I:O ratio indicates enhanced posterior deposition in the nasal cavity. 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. A higher U:L ratio indicates enhanced delivery of radioaerosol into the upper portions of the nasal cavity.

**Data Analysis:** All group data are presented as mean  $\pm$  standard deviation. Statistical analyses comparing the regional deposition pattern (I:O and U:L ratios) for the nebulizer versus the aqueous spray pump were performed using the Wilcoxon-signed rank test. P-values less than 0.05 were judged to represent significant differences.

## RESULTS

Results of the regional analysis in terms of the I:O and U:L ratios using the nebulizer and nasal spray pump are presented in Table 1. Mean I:O ratios were significantly higher for the nebulizer, averaging  $0.258 \pm 0.148$ , compared to the spray pump which averaged  $0.063 \pm 0.052$  ( $p < 0.03$ ). The higher I:O ratio indicated that deposition in the posterior region of the nasal cavity was enhanced with the nebulization method compared to the spray pump.

Mean U:L ratios were significantly higher with the nebulizer, averaging  $0.444 \pm 0.177$ , compared to the spray pump which averaged  $0.315 \pm 0.111$  ( $p < 0.03$ ). These results indicated that the

Table I

Regional analyses comparing the deposition pattern from aqueous nasal spray pumps and nasally nebulized solutions. Counts per pixel per time were determined for inner, outer, upper and lower zones in each aerosol image. Inner to outer (I:O) and upper to lower (U:L) ratios were then calculated. A larger I:O or U:L ratio indicates enhanced penetration of aerosol into either the inner or upper regions of the nasal cavity.

Volunteer	Nebulizer	Spray Pump	Nebulizer	Spray Pump
	I:O	I:O	U:L	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
<b>Average</b>	<b>0.258</b>	<b>0.063</b>	<b>0.444</b>	<b>0.315</b>
<b>Standard Deviation</b>	<b>0.148</b>	<b>0.052</b>	<b>0.177</b>	<b>0.111</b>

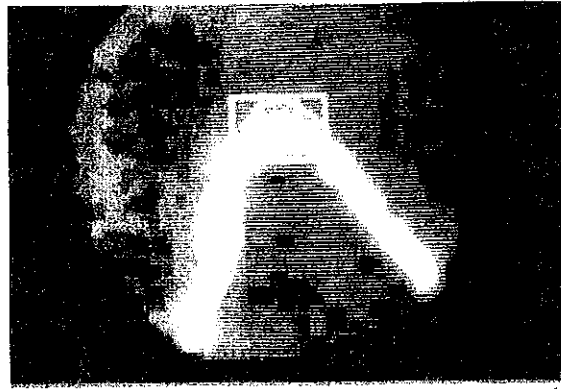
nebulizer deposited more aerosol in the upper portion of the nasal cavity compared to the spray pump.

These results confirm previous deposition studies showing that nasal spray pumps deposit aerosol primarily in the anterior portion of the nasal cavity (3,7,8). No other studies have been performed that compare the regional deposition pattern from nebulizers and spray pumps.

## DISCUSSION

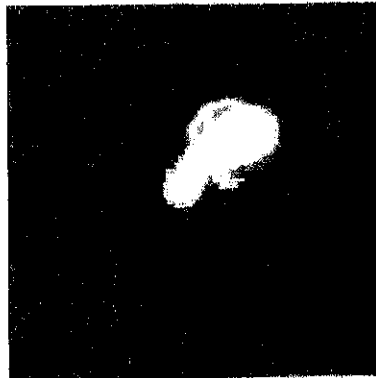
In the past, nebulizing solutions for nasal delivery has been an unattractive proposition since nebulizers were large and cumbersome. This "proof of concept" study used an air blast nebulizer with a compressed air source which suffered from these limitations. However, there are now hand held delivery systems capable of atomizing solutions such that a dose of drug could be delivered into the nasal cavity in a single breath. For example, AERx<sup>®</sup> (Aradigm Corporation, Hayward, CA) or the micro-dose aerosol generator (AeroGen, Inc., Sunnyvale, CA) produce fine, slow-moving droplets in short, individual pulses. Such aerosols have approximately the same characteristics as the nebulized aerosols we investigated. Typical mass median aerodynamic diameters of 2.8 and 3.2 $\mu$ m for the AERx<sup>®</sup> and AeroGen systems respectively have been reported (9,10). Delivering doses of fine droplets in a single inhalation with a compact system would provide a way of targeting regions of the nose which cannot be accessed with existing aqueous spray pump technology.

No previous studies have utilized a xenon ventilation image registered with nasal aerosol images for regional analysis. Defining the regions of interest with the ventilation scan ensures that the same zones are compared in each volunteer's nebulizer and spray scintigraphy image. Since a gas permeates all areas of the nasal cavity, the outline of the entire nasal cavity can be defined (Figure 4A). Theoretically all regions into which xenon can diffuse should be accessible to an appropriate aerosol. The aqueous spray was not able to achieve such coverage (Figure 4B)



(a)

**Figure 4.** Lateral ventilation and aerosol images from a typical volunteer. 4A shows the outline of the nasal cavity and regions of interest drawn on the inhaled  $^{133}\text{Xenon}$  image. 4B and 4C show the radioaerosol image from the nasal spray pump and nebulizer respectively. The inner and outer regions of interest are defined.



(b)



(c)

while the nebulizer was shown to cover more of this target area (Figure 4C). Xenon ventilation scans also allow the low cost exclusion of subjects with atypical nasal cavities or confounding disease states which could influence aerosol deposition. This is important if scintigraphy is used as a surrogate for *in vivo* bioequivalence studies comparing two nasal products.

This study is the first to quantitatively demonstrate that nebulized delivery significantly improves the distribution of aerosol within the nasal cavity. Larger I:O ratios with the nebulizer indicated that aerosol is deposited more deeply into the nasal cavity. Greater U:L ratios with the nebulizer showed that aerosol is preferentially deposited in upper regions of the nose compared to the spray pump. Nebulizers are therefore capable of coating a greater surface area of the nasal cavity including the turbinates which are highly vascularized projections into the nasal cavity. Their whole surface represents an underutilized target for drug delivery since aqueous spray pumps probably deposit aerosol primarily on the leading edge of the middle turbinate leaving the rest uncoated. These findings may have significant implications for optimizing delivery of therapeutic agents for local or systemic activity.

Administering drugs by nebulizer into the nose could enhance deposition of drug in the pharynx and lungs compared to an aqueous spray. We could not estimate lung penetration since simultaneous imaging of the nose and lungs was impossible due to the gamma camera's limited field of view. Significant lung penetration may or may not be a serious limitation depending on the drug that is being administered and the characteristics of the aerosol which is delivered. The effect of mucociliary clearance on the fate of deposited drug particles should be explored since the literature and our experience suggests that particles deposited towards the back of the nose are cleared faster. The clearance of particles deposited higher in the nasal cavity is less certain.

Further investigations with aerosolized medications are needed to determine the clinical importance of altering the deposition profiles by changing the spray pattern of nasally inhaled products. Such information would provide a rational basis for *in vitro* tests on nasal sprays required by FDA.

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