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Deposition of aerosols delivered by nasal route with jet and mesh nebulizers

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ABSTRACT

Purpose: To quantify the amount of aerosol deposited in different parts of the airways with a commercially available nasal sonic jet nebulizer (NJN) using a sound effect, and to compare its performance with a new nasal mesh nebulizer (NMN).
Methods: Seven healthy non-smoking male volunteers aged 21–36 years with a mean weight of 77 ± 10 kg were included in this single-center study. Both nebulizer systems were loaded with ^{99m}Tc-DTPA and scintigraphies were performed with a gamma camera. Particle size distribution of the aerosols produced by the two nebulizer systems was measured.
Results: There was no statistical difference between the two nebulizers in terms of fraction of particles smaller than 5 μm (44 ± 4% vs 45 ± 2%) ($p > 0.9$). Aerosol deposition in the nasal region was 73 ± 10% (% of aerosol deposited in airways) with the NJN, and 99 ± 3% with the NMN ($p = 0.01$). Total nasal deposition was 9.6 ± 1.9% of the nebulizer charge with the NJN and 28.4 ± 8.9% with the NMN ($p = 0.01$). 0.5 ± 0.3% of the nebulizer charge was deposited in the maxillary sinuses with the NJN, compared to 2.2 ± 1.6% with the NMN ($p = 0.01$).
Conclusion: Although the two nebulizers had the same particle size, NMN significantly improved aerosol deposition in nasal cavity and prevents deposition into the lungs.

1. Introduction

The treatment of nasal infections is sometimes challenging, and one strategy is to deliver antibiotics by aerosol directly to the site of infection, as in the treatment of bronchial colonization by *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients. Chronic sinusitis is one of the most commonly diagnosed chronic nasal illnesses and the site of infection is located beyond the nasal valve. There are three targets for aerosol drug to treat sinusitis: the first is the middle meatus which is a major site of drainage of sinuses and ethmoid, the second is the superior and posterior regions of the nasal cavity and the third target is the maxillary and ethmoid sinuses (Laube, 2007).

The FDA has released draft guidance for pharmaceutical companies emphasizing the importance of characterizing the site of aerosol deposition in patient airways to assess the efficiency of treatment in terms of the dose/response relationship (FDA, 2003). However, this is particularly difficult to demonstrate for sinusitis treatment due to the technology of nasal device which does not allow targeting the specific anatomical region in the nasal cavity.

Sprays can be used to deliver drugs to the nasal cavity, but the nasal sprays currently available on the market are limited by their formulations and technologies. The drug fraction delivered beyond the nasal valve is low (Suman et al., 1999), and most deposited drug is quickly removed by mucociliary clearance and eventually eliminated through the digestive tract (Hwang et al., 2006).

The advantage of nasal nebulization is that it improves deposition below the nasal valve in comparison to nasal sprays (0.21 vs 0.07 in term of ratio between aerosol deposited in the posterior third of nasal cavity and the anterior third of the nasal cavity beginning at the nostril) (Suman et al., 1999). However, maxillary sinuses communicate with the nasal cavity via small ostia (2–5 mm diameter) and they are poorly ventilated, which limits aerosol penetration into the maxillary sinuses. Specific nasal jet nebulizers using a

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sound (nasal sonic jet nebulizer), with a frequency of 100 Hz, have been developed by manufacturers to improve aerosol deposition in the maxillary sinuses (Guillerm et al., 1959). The sound generates a positive pressure from the ostium to the maxillary sinuses allowing the gas exchange with the maxillary sinuses: it can be considered as a Helmholtz resonator (Maniscalco, 2006). In vitro and in vivo studies have demonstrated the benefit of applying this sound for maxillary sinus ventilation and deposition (Maniscalco et al., 2006; Möller et al., 2008; Durand et al., 2001; Valentine et al., 2008) increasing the aerosol deposition into maxillary sinuses by a factor two (Möller et al., 2009). Specific nasal sonic jet nebulizers using sound effect are therefore the best option for targeting antibiotic aerosols to the site of infection in the case of chronic rhinosinusitis.

On the other hand, the major disadvantage of nasal jet nebulizer devices is that they deliver a significant part of the aerosol into the lungs (33–58%) (Suman et al., 1999), raising the risk of side effects, as previously reported in clinical cases with oil (Decocq et al., 1996) and not allowing the demonstration of the efficiency of treatment in terms of topical dose/response relationship (FDA, 2003).

The new generation of nebulizers, operating through a vibrating or non-vibrating mesh, which have proved to be efficient for aerosol delivery to the lungs, have not yet been developed for nasal applications.

Furthermore, while aerosol deposition in the patient's lungs has been measured using standard jet nebulizers through the nasal route (Suman et al., 1999; Djupesland et al., 2004), to our knowledge there are no studies describing lung deposition after nasal inhalation using a nasal sonic jet nebulizer equipped with a sound system specifically designed for nasal treatments, or using a mesh nebulizer.

The aim of the present work is to quantify by gamma camera the amount of radioactive aerosol deposited in the different parts of the airways of seven healthy volunteers with a commercially available nasal sonic jet nebulizer using a sound effect, and to compare its performance with a new nasal mesh nebulizer designed to avoid lung deposition.

2. Materials and methods

2.1. Human volunteers

Seven healthy non-smoking male volunteers aged 21–36 years with a mean weight of 77 ± 10 kg and a mean height of 1.81 ± 0.03 m were included in this single-center study. The study protocol was approved by the Ethics Committee of the hospital and University of Louvain Medical School, and by the regulatory authorities. In accordance with the Declaration of Helsinki and with current guidelines for Clinical Good Practice, all the volunteers gave their written informed consent before recruitment. The participants were in good health according to various tests performed during the screening visit (e.g. physical examination, vital signs, medical history). Exclusion criteria were the following: significant vascular or cardiac disease, history of allergy (such as allergic rhinitis), asthma, and history of ear nose and throat (ENT) surgery (reconstructive or functional) or of sinonasal pathology (nasal polyposis, chronic rhinosinusitis). Clinical examination was completed by an ENT specialist.

A right nasal septum deviation was detected in patient 3 and a right nasal bone septum in patient 5. These observations were considered as anatomical variants which may be encountered in a general non-selected population, and these two patients were therefore included in the study.

The study was conducted in three steps for each volunteer: (1) selection visit and medical examination, (2) scintigraphic study with nasal sonic jet nebulizer, and (3) scintigraphic studies with krypton gas (^{81m}Kr) and new nasal mesh nebulizer. There was an interval of one month between steps 2 and 3. None of subjects used any medication that might have an effect on the upper airways during the study protocol.

2.2. Nebulization systems

Two nasal nebulizer systems were used: a nasal sonic jet nebulizer (Atomisor NL11S® sonic, DTF-Medical, France) and a new nasal mesh nebulizer (DTF-Aerodrug, France).

The Atomisor NL11S® sonic jet nebulizer was used with an AOHBOX® (DTF-Medical, Saint Etienne, France) compressor generating an additional sound at a frequency of 100 Hz (Fig. 1). This sonic aerosol was administrated from both nasal plugs and was inhaled by the patient during his inspiratory phase.

The new nasal mesh nebulizer (Fig. 1) was the Aeroneb Solo® mesh nebulizer (Aerogen, Galway, Ireland) connected to a special new compressor (DTF-Aerodrug, Tours, France) designed to avoid lung deposition. The special compressor administrates a constant air flow rate transporting the aerosol to the first nasal plug and aspirates the same air flow rate from the second nasal plug. As consequence, aerosol was administrated to the first nostril and was aspirated through the second nostril with the same air flow rate avoiding a nasal breath (closed system). Aerosol was continuously administrated into nasal cavity during mouth breathing of the patient.

Disposable jet and mesh nebulizers were used, i.e. one pair per volunteer.

The particle size distribution of the aerosols produced by each nebulizer system was measured (Spraytec, Malvern, UK) to determine the volume mean diameter (VMD) and the fine particle fraction (percentage of particles with a diameter smaller than 5 μm predicting the fraction of aerosol likely to be deposited in the lungs).

2.3. Aerosol inhalation

Both nebulizer systems were loaded with 3 ml of ^{99m}Tc-DTPA (TechneScan DTPA, Mallinckrodt Medical, Petten, The Netherlands), and the activity placed in each nebulizer reservoir, measured with a CRC-12 Capintec radioisotope calibrator (Pittsburgh, PA), was 75 ± 4 MBq. Before aerosol inhalation, volunteers were trained to inhale the aerosol through the nose and exhale through the mouth with the nasal sonic jet nebulizer and to inhale and exhale only through the mouth with the new nasal mesh nebulizer. Absolute filters (PALL BB50TE, Pall medical, France) were connected to the nebulizer systems to avoid ambient aerosol contamination and to measure total activity recovered from the airways. An absolute filter was connected to the mouthpiece of both nebulizers and an additional filter was connected to the nasal sonic jet nebulizer to measure aerosol leakage. No ambient and surface contamination was detected. The duration of nebulization with both nebulizers was limited to 10 min.

2.4. ^{81m}Kr gas inhalation

^{81m}Kr gas (^{81}Rb–^{81m}Kr generator, Covidien, Petten, The Netherlands) was continuously administered through the nostrils to measure nasal and lung ventilation. The ^{81m}Kr generator was connected to an AOHBOX® box compressor generating a 100 Hz sound to image maxillary sinuses (Möller et al., 2009). Images were acquired without and later with additional sound during 2 min of gas administration.

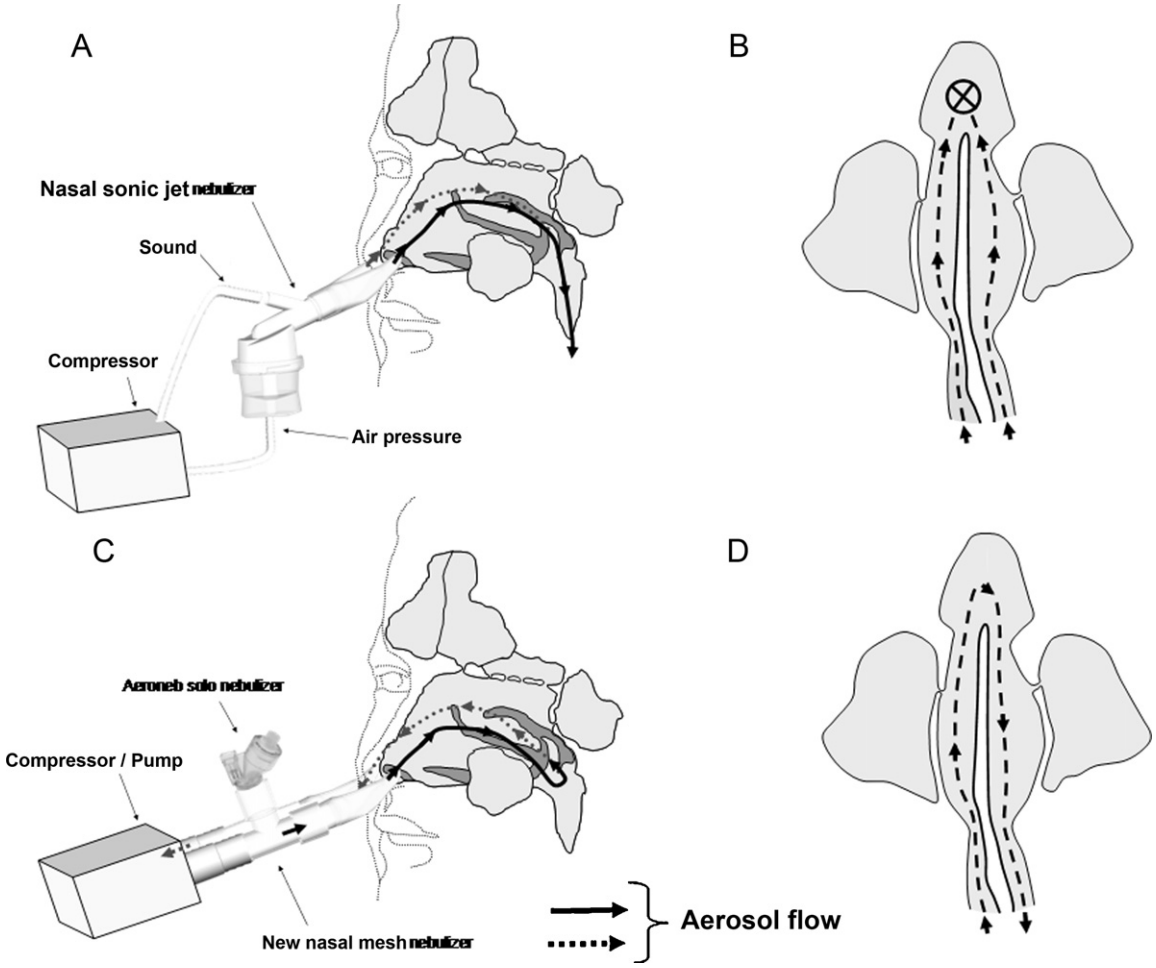

Fig. 1. Graphical representation of nasal sonic jet (A) and new nasal mesh (C) nebulizers operation and superior view of aerosol flow rate in nasal cavity (B: nasal sonic jet nebulizer, D: new nasal mesh nebulizer).

2.5. Image acquisition

2.5.1. Technical conditions

In all volunteers, scintigraphy was performed using a planar single detector gamma camera (STARPORT 400 AC/T, GE, Horsholm, Denmark) equipped with a 390 mm low-energy high-resolution collimator, calibrated monthly for uniformity (UFOV 370 mm and CFOV 278 mm). One-minute images were acquired for the devices (including nebulizer and filters) and 2-min images of the volunteers' airways using a 128×128 matrix. The spatial resolution of this system is 5.3 mm at 10 cm.

2.5.2. Aerosol deposition imaging

Immediately after nebulization, images were acquired. The volunteer was seated in front of the acquisition field of the camera and four aerosol images were recorded: (1) lateral view of the head to image aerosol deposition in the nasal cavity, (2) anterior view of the head to image aerosol deposition in the nasal cavity and sinuses, (3) posterior view of the thorax to image aerosol deposition in the stomach and lungs, and (4) residual activity in the nebulizer device including filters and tubing.

2.5.3. ^{81m}Kr gas imaging

The volunteer sat in front of the acquisition field of the camera and four gas images were recorded: (1) lateral view of the head without additional sound to image the nasal cavity profile, (2A) anterior view of the head without additional sound to image the nasal cavity without sinuses, (2B) anterior view of the head with additional sound to image the nasal cavity with sinuses, and (3) posterior view of the thorax to image the lungs.

2.6. Image processing and analysis

2.6.1. Aerosol deposition in the upper airways and lungs

DICOM3 native gamma camera images were analyzed with Siemens software. Activity deposited in the airways was calculated by the activity balance method based on the difference between the activity loaded in the nebulizer and residual activity (Aerosol Image 4) taking into account gamma camera attenuation, background and radioactive decay. Regions of interest (ROIs) of the nasal cavity (Gas Image 1) and lungs (Gas Image 3) were defined using Siemens processing software from ^{81m}Kr ventilation images and were applied to aerosol images. Activity in the upper airways was defined by adding the activity measured in the nasal cavity (Aerosol Image 1) and the activity measured in the stomach (Aerosol Image 3), on the assumption that activity in the stomach results from nasal clearance and pharyngeal deposition during inhalation.

Results were expressed in terms of activity loaded in the nebulizer, and the ratio between the upper airways aerosol deposition and lung deposition was calculated.

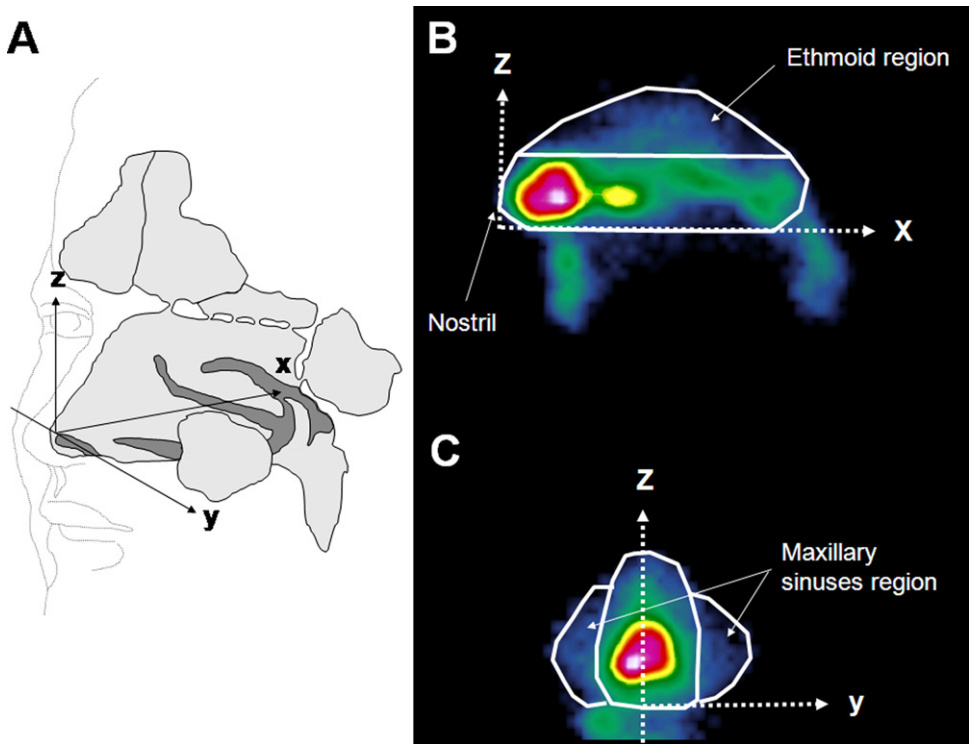

Fig. 2. Graphical representation on the nasal cavity and region of interest (A: diagram of nasal cavity and the three axes (*X*, *Y*, *Z*) used to analyse the activity distribution obtained by gamma imaging; (B) lateral view of aerosol deposited into nasal cavity and region of interest; (C) Anterior view of aerosol deposited into nasal cavity and region of interest).

2.6.2. Aerosol distribution in the nasal cavity

The gamma camera images were analyzed with the Image J software package (Image J1.43U, National Institutes of Health, USA). The results of this analysis were compared with those obtained using dedicated nuclear medicine processing software (Bartec Medical Systems, Farnborough, UK) and showed comparable activity profiles (data not shown), validating the Image J1.42 software package to analyze activity distribution in the airways.

The ROIs of maxillary sinuses (Fig. 2) were defined by subtracting Gas Image 2B obtained from ^{81m}Kr gas with sound (nasal cavity and maxillary sinuses) from Gas Image 2A obtained from ^{81m}Kr without sound (nasal cavity only). The ROI of the ethmoid region was defined from the lateral view with ^{81m}Kr (Gas Image 1) as the upper half of the nasal airway. These ROIs (Fig. 2) were applied on aerosol images and the results were expressed in terms of activity loaded in the nebulizer taking into account background radiation and physical decay of radioactivity.

The distribution of the aerosol deposited in the nasal cavity was also analyzed on three axes (*X*, *Y*, *Z*): *X*—from nostrils to cavum; *Y*—from the floor to the upper cavity; *Z*—from nose column to the extremity of the maxillary sinuses (Fig. 2). This distribution was normalized.

2.7. Statistical analysis

Statistics were performed using Statxact®, Cytel Software Corporation, Version 3.0.2. A non-parametric paired Wilcoxon's signed rank test was used to compare the data generated from the in vivo study and a non-parametric Mann–Whitney to compare the particle size obtained from the nebulizers. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Particle size distribution

Volume median diameters of $5.6 \pm 0.5\,\mu m$ and $5.6 \pm 0.3\,\mu m$ were obtained for the nasal sonic jet and new nasal mesh nebulizers respectively. The fraction of particles smaller than 5 μm was $44 \pm 4\%$ for the nasal sonic jet nebulizer and $45 \pm 2\%$ for the new nasal mesh nebulizer. There were no statistical differences between the two nebulizers in terms of VMD and fraction of particles smaller than 5 μm ($p > 0.9$, $n = 42$).

3.2. Gas ventilation

Upper and lower airways were equally well-ventilated in all volunteers (Fig. 3). Gas activity in the maxillary sinuses was observed in all volunteers when a sound was generated but was not without sound generation (Fig. 3), demonstrating the gas penetration due to sound effect. These results demonstrate the opening of the sinusal ostia and allowed anatomical ROIs of the maxillary sinuses to be identified.

3.3. Aerosol deposition

Liquid drop accumulation in the nose with lip contamination was detected after nebulization in 3/7 subjects (Fig. 3, Mesh 1) for both nebulizers. Activity deposited in the lips was added with the residual activity.

Fig. 3 shows gas and aerosol images obtained from volunteer 1, highlighting differences between gas and aerosol deposition and between the two nasal nebulizer systems.

Aerosol deposition in upper airways region was $73 \pm 10\%$ (% of aerosol deposited in airways) for the nasal sonic jet nebulizer and

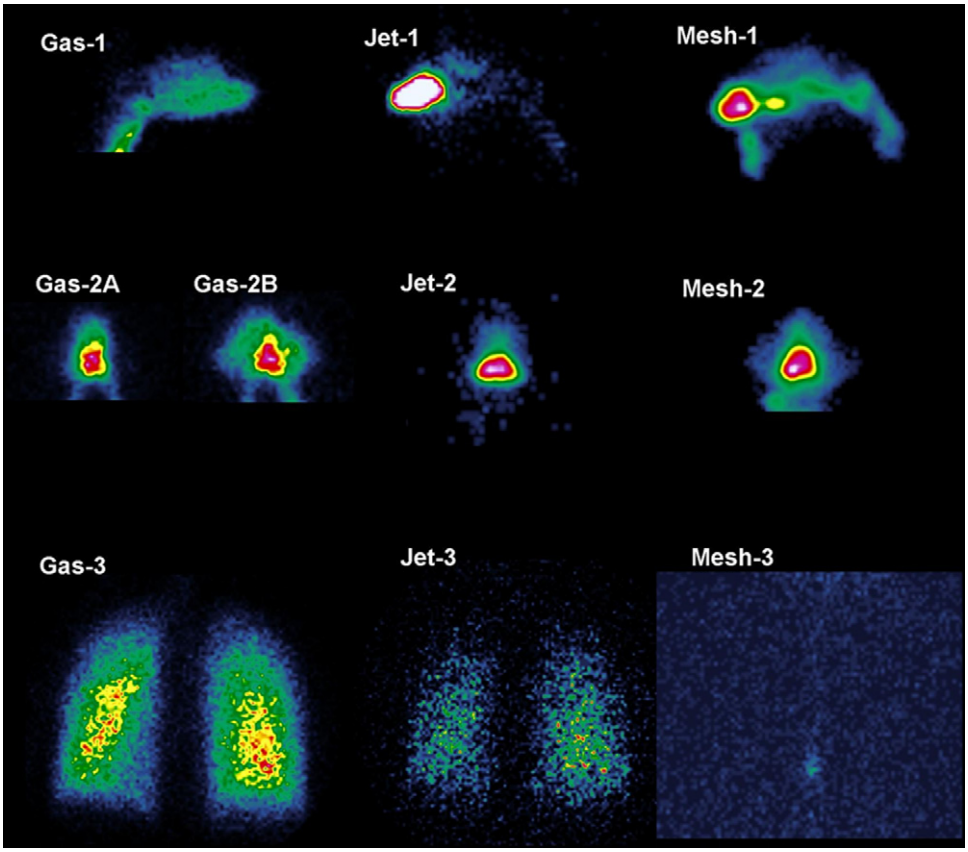

Fig. 3. Scintigraphy images obtained from the first subject with Krypton gas (Gas-1: lateral view of nasal cavity; Gas-2A: anterior view of nasal cavity without sound; Gas-2B: anterior view of nasal cavity with sound; Gas-3: posterior view of thorax), DTPA-Tc99m aerosol generated with the nasal sonic jet nebulizer (Jet-1: lateral view of nasal cavity; Jet-2: anterior view of nasal cavity; Jet-3: posterior view of thorax) and DTPA-Tc99m aerosol generated with the new nasal mesh nebulizer (Mesh-1: lateral view of nasal cavity; Mesh-2: anterior view of nasal cavity; Mesh-3: posterior view of thorax). White and red colours indicate a high activity, blue colour indicates a low activity and black colour indicates no activity. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

$99 \pm 3\%$ for the new nasal mesh nebulizer (Table 1). Aerosol deposition in the lungs (% of aerosol deposited in airways) was $27 \pm 10\%$ for the nasal sonic jet nebulizer and $1 \pm 3\%$ for the new nasal mesh nebulizer. With the new nasal mesh nebulizer, only volunteer 5 had some aerosol deposition in the lungs which explains the standard deviation obtained with the new nasal mesh nebulizer results. There was a statistical difference in terms of aerosol distribution (upper and lower airways) between nasal sonic jet and new nasal mesh nebulizers ($p = 0.01$) showing better targeting of the upper airways with the new nasal mesh nebulizer.

Total nasal deposition (activity deposited into the nasal cavity and the stomach) was $9.6 \pm 1.9\%$ of the nebulizer charge for the nasal sonic jet nebulizer and $28.4 \pm 8.9\%$ for the new nasal mesh nebulizer ($p = 0.01$). The aerosol deposited into the lungs in term of nebulizer charge was statistically higher with the nasal sonic jet nebulizer than with the new nasal mesh nebulizer ($3.7 \pm 1.7\%$ vs $0.3 \pm 0.9\%$) ($p = 0.03$). There was more activity measured in the stomach with the new nasal mesh nebulizer ($p = 0.03$).

Only $0.5 \pm 0.3\%$ of the nebulizer charge was deposited in the maxillary sinuses with the nasal sonic jet nebulizer, compared to $2.2 \pm 1.5\%$ with the new nasal mesh nebulizer ($p = 0.01$) (Fig. 3), corresponding respectively to 5% and 7% of the aerosol deposited in the nasal cavity. Similar low values were measured in the ethmoidal region (Fig. 3) with both nasal sonic jet and new nasal mesh nebulizers ($1.1 \pm 0.9\%$ and $3.4 \pm 1.8\%$ of nebulizer charge respectively), but showing a higher deposition of aerosol in the ethmoidal and maxillary sinus regions with the new nasal mesh nebulizer ($p = 0.01$).

Aerosol distribution deposition along the *X*-axis showed a maximum value 2 cm from the nostril for both nebulizers, which may correspond to deposition in the nasal valve region (Fig. 4). The two nebulizers had a similar distribution profile showing a rapid decrease in deposition from 2 to 3 cm following the peak value and a slower decrease from 3 to 10 cm (0 cm being the extremity of the nose).

Aerosol distribution deposition along the *Z*-axis showed an identical profile for both nebulizers, but the maximum obtained with the new nasal mesh nebulizer was nearer the nasal floor than the nasal sonic jet nebulizer (0.75 cm vs 1.2 cm) (Fig. 5).

Aerosol distribution along the *Y*-axis showed an identical profile for both nebulizers with high deposition in the nose column (0 cm) and decreased deposition in the two opposite directions of the *Y*-

Table 1
In vivo results with nasal sonic jet and new nasal mesh nebulizers expressed as a percentage of the nebulizer charge (1) and in terms of the total aerosol fraction deposited in subjects' airways (2) (nasal cavity including ethmoidal and maxillary sinuses; upper airways including the nasal cavity and stomach).

	Nasal cavity[1]	Ethmoidal sinus[1]	Maxillary sinuses[1]	Lung[1]	Stomach[1]	Upper airways[2]	Lung[2]
Nasal sonic jet nebulizer	9.6 ± 1.9%	1.1 ± 0.9%	0.5 ± 0.5%	3.7 ± 1.7%	0.0 ± 0.1%	73 ± 10%	27 ± 10%
New nasal mesh nebulizer	28.4 ± 8.9%	3.4 ± 1.8%	2.2 ± 1.5%	0.3 ± 0.9%	1.8 ± 2.2%	99 ± 3%	1 ± 3%

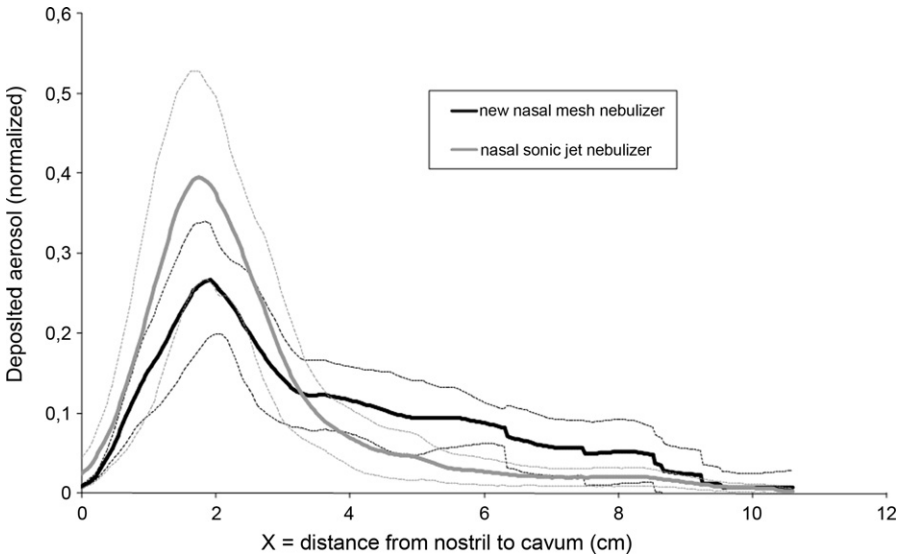

Fig. 4. Aerosol distribution in nasal cavity from nostril to cavum (normalized data).

axis (Fig. 6). Similar distribution of deposited aerosol in the nasal cavity was obtained with the two nebulizer systems.

4. Discussion

Nebulizers are the only nasal devices available on the market to treat sinusitis with antibiotics. Based on previous studies (Maniscalco, 2006; Möller et al., 2008, 2009; Durand et al., 2001; Valentine et al., 2008), specific nasal jet nebulizers using sound effects are currently the best option for targeting antibiotic aerosols to the site of infection in case of chronic rhinosinusitis. This study demonstrates that aerosols produced by these specific nasal sonic jet nebulizers using sound effect are deposited in the anatomical targets to treat sinusitis. Based on previous studies comparing nebulizers performances designed to deliver the aerosol into the lungs, results obtained in this study could be different using different nasal nebulizers such as Pari sinus nebulizer (Pari, Starnberg, Germany), Sinusaero (Sinusdynamics, Westlake Village, USA) or Nebula nebulizer (Markos, Monza, Italy).

Previous studies (Suman et al., 1999; Djupesland et al., 2004) measured lung deposition of about 33% in terms of total aerosol deposited in the patients' airways, but these studies did not use a specific nasal sonic jet nebulizer using a sound effect which is designed to improve aerosol delivery in the maxillary sinuses. In our study, based on the (Möller et al., 2008) method using ^{81m}Kr gas, we used a specific nasal sonic jet nebulizer with sound effect that enables gas to penetrate the maxillary sinuses and hence allows anatomical regions to be determined. With the nasal sonic jet nebulizer with sound effect, aerosol deposited in volunteers' lungs was similar to results obtained from Pari jet nebulizer without sound effect (Djupesland et al., 2004) ($27 \pm 10\%$ vs $22 \pm 8.1\%$), demonstrating that the sound effect has no significant effect on lung deposition. Therefore, despite a more efficient targeting of the upper airways with nasal sonic jet nebulizers, the risk of toxic effects due to lung deposition persists. By contrast, the new nasal mesh nebulizer dramatically reduced the inhaled fraction deposited in the lungs: 27% of the aerosol deposited was located in the lungs with the nasal sonic jet nebulizer, compared to only 1% with the new

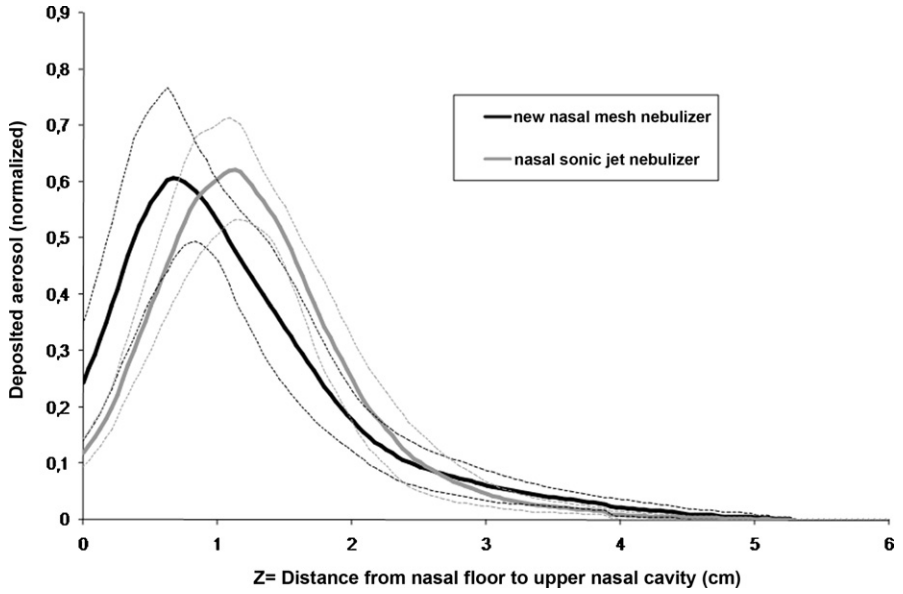

Fig. 5. Aerosol distribution in nasal cavity from nasal floor to upper nasal cavity (normalized data).

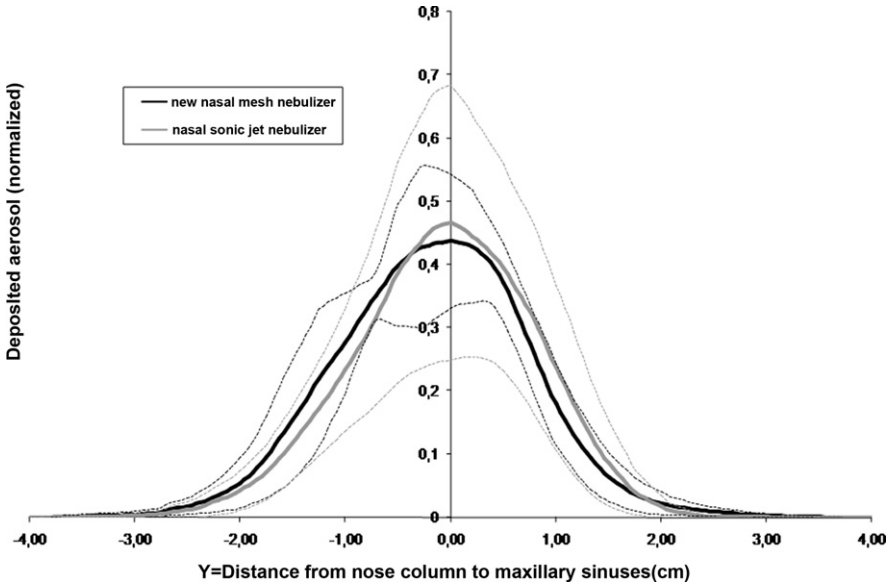

Fig. 6. Aerosol distribution in nasal cavity from nose column to maxillary sinuses (normalized data).

nasal mesh nebulizer. This clearly demonstrates a higher anatomical selectivity with the new device. It also indicates that particles sizes distributions are identical, it does not mean that the in vivo distribution would be identical (e.g. our new nasal mesh nebulizer). Other parameters need to be taken into account to predict aerosol deposition into patient airways. These two nebulizer systems produce the same particle size but operate differently in term of aerosol kinetic. The aerosol generated by the nasal sonic jet nebulizer is inhaled by the patient and penetrates into nasal cavity and goes to patient lungs to allow patient breath (Fig. 1). The aerosol generated by the new nasal mesh nebulizer and its associated compressor penetrates by the first nostril and goes out to the second nostril. The patient cannot inhale by the nose because the nebulizer system and the cavity's anatomy are a closed system. The patient has to breathe through the mouth, then the soft palatine closes the nasal cavity avoiding aerosol penetration into the lungs.

Furthermore, the new nasal mesh nebulizer produced more deposition in terms of volume of liquid (27% vs 9%, i.e. 0.81 mL vs 0.27 mL) in the nasal cavity. The amount of aerosol deposited in each part of the nasal cavity was higher with the new nasal mesh than the nasal sonic jet nebulizer. All the figures (Figs. 4–6) representing the aerosol distribution on each axis show a similar aerosol distribution deposition in the nasal cavity. Measurement of aerosol deposited in the regions of interest demonstrates that the new nasal mesh nebulizer improves aerosol delivery in the nasal cavity by a factor of 3, in the maxillary sinuses by a factor of 4, and in the ethmoid region by a factor of 3.

This difference in term of amount of deposited aerosol can be explained by the residual volume remaining into the nebulizer reservoir which is lower with mesh nebulizer in comparison with jet nebulizers (Vecellio, 2006) and by the aerosol kinetic difference between the two nebulizers (Fig. 1). The new nasal mesh nebulizer has administrated continuously the aerosol in the nasal cavity by contrast to the nasal sonic jet nebulizer administrating the aerosol only during inspiratory phases. As consequence, there was less aerosol leakage with the new nasal mesh nebulizer system in comparison with the nasal sonic jet nebulizer.

The highest deposition in the nasal cavity was located in the first two centimetres of the nose (28% with the new nasal mesh nebulizer and 44% with the nasal sonic jet nebulizer, in terms of aerosol deposited in the nasal cavity), which can be explained by the nasal valve restriction increasing impaction (Fry and Black, 1973) and vortex regions downstream of the nasal valve (Croce et al., 2006). Only $0.5 \pm 0.3\%$ of the nebulizer charge was deposited in the maxillary sinuses, corresponding to around 5% in terms of nasal deposition. These results are consistent with previous studies using a cadaver head (Valentine et al., 2008) or volunteers (Möller et al., 2009) measuring maxillary deposition in a similar range (3–5% in terms of nasal deposition). Similar low deposition results have been obtained in the ethmoid region corresponding to $1.1 \pm 0.9\%$ of the nebulizer charge and 11% of the nasal deposition. The precise localisation of aerosol deposition in the different anatomical parts of the nasal cavity is very difficult to determine due to the close connection between small anatomical regions (Aggarwal et al., 2004), in particular for the aerosol fraction reaching beyond the nasal valve, and also due to the limited spatial resolution of gamma camera imaging. In previous studies, regions of interest were determined in terms of pixel areas to separate anterior, posterior, upper and lower regions of the nasal cavity (Suman et al., 1999). While this method is adequate for comparing large differences in terms of aerosol distribution, it does not give sufficiently precise information in terms of aerosol distribution in the nasal cavity geometry, which could be important for understanding the physical phenomena of aerosol deposition and associated clinical effects. Our study produced a cartography of aerosol distribution on the three axes (Fig. 1), and it compared the aerosol distribution of two nasal devices producing similar aerosols in terms of particle size, but operating differently. Furthermore, the detailed analysis of the aerosol distribution in the nasal cavity did not show significant differences between jet and mesh nebulizers.

Aerosol images obtained in our study included analysis of aerosol clearance in the 10 min after nebulization. Three different clearance mechanisms have previously been described (McLean et al., 1984; Vidgren and Kublik, 1998). First, there is a very rapid clearance phenomenon due to swallowing or run out of deposited particles into the rhinopharynx and then into the stomach, particularly for large volumes of deposited liquid particles. This could explain the difference between the two nebulizers in terms of stomach and nasal floor deposition. The higher stomach activity with the new nasal mesh nebulizer is probably related to the larger volume of aerosolized solution penetrating the airways (0.81 mL vs 0.27 mL) followed by rapid clearance. Fig. 5 shows the aerosol dis-

tribution from the floor to the upper nasal airways. In the first part of this nasal distribution, values included high deposition in the nasal valve region, as shown in Fig. 4. The difference in abscissa values for the maximal activity between the two nebulizers could be explained by the rapid clearance phenomenon with the new nasal mesh nebulizer which increased the activity value in the first part of the Z abscissa. The following clearance phases occur after 15–30 min of aerosol deposition and thus were not considered in this study.

In conclusion the commercial nasal sonic jet nebulizer (Atomisor NL11S® sonic) using a sound effect is adapted to deposit the aerosol in the anatomical targets to treat sinusitis but it delivers a significant part of the aerosol into the lungs (27% in terms of aerosol deposited in the airways). Although the new nasal mesh nebulizer generates the same particle size, it significantly improves peripheral aerosol deposition in the nasal cavity without deposition in the lungs. Furthermore, it increases aerosol deposition in the nasal cavity by a factor of 3, including maxillary sinuses and the ethmoidal region. This study validates a new nasal mesh nebulizer that could be used in clinical trials to test the efficiency of local drug delivery in accordance with FDA recommendations.

Conflict of interest

S. Le Guellec, L. Vecellio and G. Chantrel are employees of la Diffusion Technique Française.

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