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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The FDA has released draft guidance for pharmaceutical companies emphasizing the importance of characterizing the site of aerosol deposition in patient airways to assess the efficiency of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.