Clinical potential of pulsating aerosol for sinus drug delivery

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There is a high incidence of nasal disorders including chronic rhinosinusitis (CRS), affecting ~ 14% of the total population. However, a topical treatment regimen shows only modest efficacy, and drug delivery to the posterior nose, osteomeatal area, and paranasal sinuses is still a challenge. Therefore, the primary treatment option of CRS is functional endonasal sinus surgery (FESS). Most nasally administered aerosolized drugs are efficiently filtered by the nasal valve and do not reach the sinuses, the site of chronic inflammation. Sinus ventilation, nasal and paranasal aerosol deposition can be achieved by using a pulsating airflow, offering new topical treatment options for nasal disorders. Inhalation studies in nasal casts and in healthy volunteers have shown up to 8% of the nasally deposited drug within the sinuses, which could not be achieved using nasal pump sprays. In addition, compared with nasal pump sprays, retention kinetics of the radiolabel deposit in the nose was prolonged by about a factor of five. With this efficiency, topical aerosol therapies of sinus disorders can be achieved and, owing to the prolonged retention, reduced application modes are possible. This offers new treatment options of sinus-nasal disorders in comparison with or after FESS.

Keywords: chronic rhinosinusitis, clearance, paranasal sinus ventilation, pulsating aerosol, topical therapy

Expert Opin. Drug Deliv. (2010) 7(11):1239-1245

1. Introduction

Chronic sinusitis is one of the most commonly diagnosed chronic illnesses, and ~ 10 – 15% of the European and US population suffer from chronic rhinosinusitis [1,2]. Inflammation of the nasal mucosa (i.e., rhinitis), due to bacterial, fungal or viral infections, allergies, or exposure to inhaled irritants, leads to acute sinusitis and chronic rhinosinusitis (CRS) [2,3]. Chronic inflammation of the nasal mucosa results in triggering of defense reactions, mucosal swelling (including polyposis), increased mucus secretion, loss of cilia, airway obstruction and blocked sinus drainage [4]. Under these conditions, bacteria and viruses that are normally removed from the nasal cavity and sinuses may proliferate. In addition, it has been reported that impaired mucociliary clearance in patients with primary ciliary dyskinesia (PCD) or cystic fibrosis (CF) also causes chronic sinusitis [3,5], and other chronic respiratory diseases, such as asthma and chronic obstructive pulmonary disease (COPD), are linked to CRS [6,7]. Surgery, often in combination with topical and systemic medical treatment, has been the primary approach for treating CRS [3,8]. An effective topical therapy may allow treating of upper respiratory diseases before or after surgery.

The sinuses are poorly ventilated hollow organs (**Figure 1**), but both *in vivo* and *in vitro* studies have shown that nebulized drugs can be deposited into the paranasal sinuses, although at very low efficiencies [9-11]. Gas and aerosol transport into non-actively ventilated areas can result from diffusion and flow induction by pressure differences [11,12], and pulsating air flows or humming can generate such pressure gradients.

10.1517/17425247.2010.523078 © 2010 Informa UK, Ltd. ISSN 1742-5247

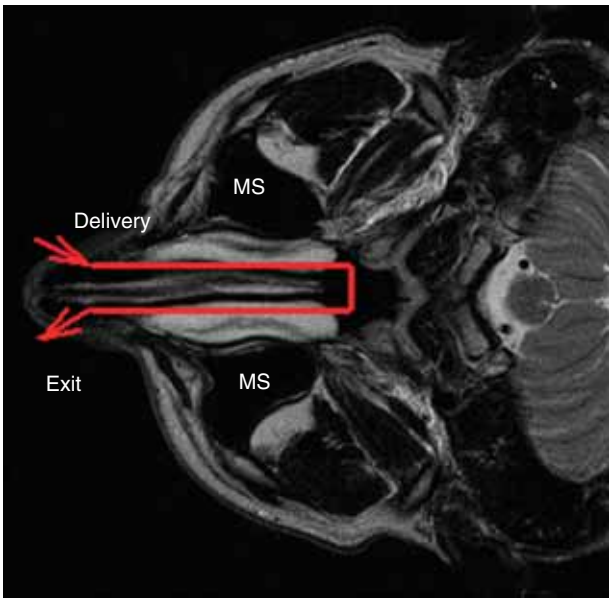

Figure 1. Slice of an axial magnetic resonance tomography scan of one subject with illustration of the MS and the pathway of the aerosol stream through the nasal cavity during pulsating aerosol delivery and closed soft palate. The nebulizer is attached to one nostril (delivery) and the flow resistor is plugged into the exit nostril.
MS: Maxillary sinuses.

2. Aerosolized drug delivery to the respiratory tract

Aerosolized drug delivery to the respiratory tract, either for topical or for systemic therapy, has been used for a long time [13]. The respiratory tract consists of several distinct units, and in general the airways (upper and lower airways) and the pulmonary (alveolar) zone can be distinguished. Air transport and delivery, and gas exchange are the main features of these distinct zones, including different diseases in these zones. The upper and lower airways seem to be distinct entities, but after a closer look there are many similarities in anatomy (both are ciliated and show mucus transport), supporting the concept of the 'united airways' [14-16]. For example, recent evidence suggests that allergic inflammation in the upper and lower airways (asthma) coexist, but their interrelationship is poorly understood [3,17]. In addition, chronic airway inflammation in CF patients is usually linked to the lower airways, but because mucus stiffening and mucus hyper-secretion also occur in the upper airways, CF patients suffer from CRS, and adequate treatment of the nasal organ is required [18]. Nevertheless, differences in structure imply specific requirements of topical drug targeting, which can be achieved in part by selecting aerosol particle size and breathing pattern, and by specific nebulizing devices.

Treating the upper airways by aerosol strategies has to deal with an extra issue, as CRS is also manifested in the sinuses, which are usually poorly ventilated. However, ventilation is a basic requirement of aerosolized drug delivery to the site of disease. Non-ventilated spaces can also occur in lung diseases, such as in emphysema, where the airways collapse owing to destruction of small airways, or in COPD and CF patients owing to mucus plugging [19,20]. Under normal conditions the sinuses are even not ventilated in healthy volunteers, and the pulsating aerosol delivery technique is one option to overcome this restriction.

2.1 Discovery of pulsating airflows for sinus drug delivery

The ventilation of secondary spaces was discovered and systematically studied by Hermann von Helmholtz, and he found resonance conditions for optimal gas exchange between the cavity and the surrounding space [21]. Interestingly, as the cavity vibrates at a certain resonance frequency, the devices were called Helmholtz resonators and were used for instrument toning. The resonance frequency is based on the geometric conditions of the cavity. Based on this knowledge, early pulsating aerosol studies for sinus drug delivery were carried out in the last century by Guillerm and colleagues [22]. Later, Kauf systematically modeled and studied the penetration ability of aerosols into secondary spaces and performed the first experiments on model cavities [12], where he got deposition efficiencies up to 1% using a bacterial aerosol. These studies were continued by Hyo *et al.* [9] and Sato *et al.* [23] using nasal casts and human cadavers, and they also could confirm deposition efficiencies between 1 and 4%.

Irrigation of the nose using high-volume squeeze bottles is an inexpensive and essentially risk-free treatment. Recent studies support the efficacy in treatment of chronic rhinosinusitis [24]. Hereby, nasal irrigations performed with large volume and delivered with low positive pressure have been shown to be more effective than saline nasal sprays. Besides nasal irrigation, one current treatment option of nasal disorders is the use of nasal pump sprays, but no significant aerosol access to the sinuses has been reported [25,26]. Recently, new nasal aerosol delivery devices have been developed, which do not use the pulsating airflow technique, such as the ViaNase (Kurve Technology, Inc., Lynnwood, WA, USA) and the Optinose (OptiNose AS, Oslo, Norway) [25,27]. These devices may improve nasal drug delivery, but the access of the aerosol to the sinuses has not yet been proved, as the droplet particle size is in the 10 μm diameter range with limited access to the sinuses and because there is only limited ventilation of the sinuses under the operating conditions of the device.

2.2 Pulsating aerosol delivery systems

A pulsating aerosol is an aerosol stream superimposed by a pulsation (sound wave). The first pulsating aerosol delivery device was developed in France by La Diffusion Technique Française (Atomisor Automatic Manosonique Aerosol, DTF,

Saint Ettiene, France), which is based on the early Guillerm studies, but there are no further dosimetric or clinical efficiency data available. In 2003 the German nebulizer company PARI developed a commercial pulsating aerosol delivery device, the PARI Sinus™ (PARI GmbH, Starnberg, Germany), which has been approved for the European market and received 510(k) clearance recently.

Standard medical nebulizers can be used for aerosol generation, such as jet nebulizers or vibrating membrane nebulizers. The nose is an efficient filter for inhaled aerosols. For efficient penetration into the sinuses, the aerosol should penetrate into the posterior nasal cavity; therefore, the aerosol should consist of smaller particles (droplets) of < 3 µm aerodynamic diameter [28]. In addition, as the dominant deposition mechanism in the nose is impaction, the flow rate should be kept moderate. The PARI Sinus pulsating aerosol device is composed of a PARI LC Star jet nebulizer with 3 µm mass median aerodynamic diameter (MMAD) (geometric standard deviation [GSD] = 2.5) and output flow rate of 6 l/min, which is necessary to operate the nebulizer. A pulsation of 44 Hz is superimposed to the aerosol stream. The nebulizer is attached to one nostril and a flow resistor is plugged into the second nostril. During delivery the subjects are instructed to close their soft palate, which directs the aerosol from the delivery nostril to the second output nostril, as illustrated in **Figure 1**, providing an aerosol pathway to the nasal airways only. The output resistor and closing the soft palate ensures optimal pressure transduction to the sinuses, and drug penetration to the lung can be prevented.

As mentioned above, these conditions are not optimal for posterior nasal aerosol penetration, therefore a further development was performed by integrating the new vibrating membrane nebulizer technology, as commercialized in the eFlow electronic nebulizer (PARI GmbH, Starnberg, Germany) [29]. Using this technology in the PARI Vibrent device, the particle size remained at 3 µm MMAD (GSD = 1.6; sharper size distribution), but the flow rate could be reduced to 3 l/min [30]. A pressure wave of 25 Hz frequency with amplitude of 20 mbar was superimposed to the aerosol stream.

2.3 Imaging sinus ventilation by ^{81m}Kr-gas delivery

^{81m}Kr-gas imaging is used in nuclear medicine to assess the ventilation of the human lung [31]. As the radiation doses are low, this technique was used to assess ventilation of the sinus cavities during pulsating gas flow [32]. ^{81m}Kr-gas was continuously ventilated through the nasal airways with and without pulsation in front of a single-head gamma camera. Without pulsation only the central nasal cavity appeared on the image (**Figure 2A**). With pulsation, the maxillary and frontal sinuses appeared on the gamma camera image (**Figure 2B**).

2.4 Assessing sinus deposition and clearance after ^{99m}Tc-DTPA aerosol administration

For testing nasal and sinus aerosol deposition and clearance, a pulsating aerosol was generated using the PARI Vibrent. In the studies by Möller *et al.*, a solution composed of ^{99m}Tc-DTPA was delivered to each nostril for 20 s, and deposition distribution was assessed by gamma camera imaging [26]. The first image recorded immediately after aerosol delivery did not show aerosol deposition in the chest or abdomen (stomach) region, confirming the tight closure of the soft palate during aerosol delivery. **Figure 3** shows anterior (**Figure 3A**) and lateral (**Figure 3B**) images of ^{99m}Tc-DTPA aerosol deposition distribution after pulsating aerosol delivery (superimposed to coronal and sagittal magnetic resonance tomography scans of the subject). The dominant fraction was deposited in the central nasal cavity. After suppressing the central nasal cavity activity using a lead shield, the ^{99m}Tc-DTPA aerosol deposition in the maxillary and frontal sinuses appears clearly (**Figure 3A**). With pulsating aerosol delivery, total deposition in the nasal cavity (including sinuses) was 71 ± 17% of the nebulized dose and 6.5 ± 2.3% of the total nose activity penetrated to the sinuses [26,32]. In addition, as shown in **Figure 3B**, there was activity access to the posterior nose, including the ethmoid and sphenoid sinuses, when using the pulsating aerosols, but not after nasal pump spray delivery.

Compared with aerosol administration by nasal pump sprays, retarded clearance kinetics after pulsating aerosol delivery was reported [26]: 50% of the dose was cleared after 1.2 ± 0.5 h and > 20% of the administered dose was retained in the nose after 6 h. The cumulative retained dose 6 h after delivery was obtained from the area under the retention curve and corresponds to 1.98 ± 0.23 normalized dose units × hour for the pulsating aerosol [26].

3. Expert opinion

3.1 Paranasal sinus ventilation, aerosol delivery and retention

Ventilation of the target site is a significant requirement for aerosol drug delivery. The efficiency of pulsating airflows for proper sinus ventilation is evident from **Figure 2**. Although no significant ventilation was detected without pulsation, ~ 50% of the total Kr-gas activity within the nasal cavity penetrated into the sinuses [32]. As pulsating airflow causes entire sinus ventilation, this fraction represents the volume of the sinuses in relation to the total nasal air volume. In addition, pulsating airflow caused a sustained release of ^{81m}Kr-gas activity from the nasal cavity and the sinuses after switching off Kr-gas delivery [33]. The authors conclude that this delay can cause an increased residence time of an aerosolized drug in the sinuses, further enhancing aerosol deposition.

Access and deposition of significant amounts of aerosol into the sinuses could not be detected using nasal pump sprays, but using pulsating aerosols ~ 6.5% of activity deposited in the nasal cavity was detected in the sinuses. This rate is lower compared with Kr-gas ventilation efficiency and may

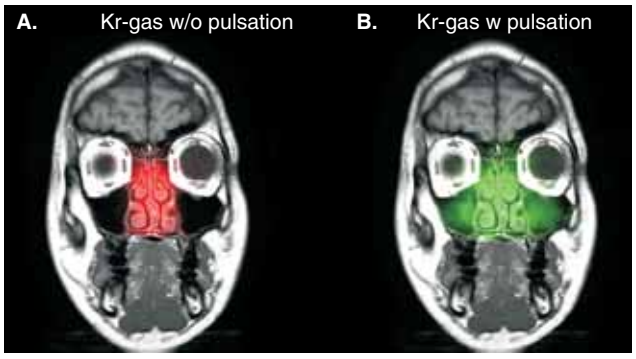

Figure 2. Superposition of anterior gamma camera images of ^{81m}Kr-gas ventilation (A) without and (B) with pulsating airflow with a coronal magnetic resonance tomography image in one subject.

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w: With; w/o: Without.

result from high aerosol deposition at the nasal entrance (nasal valve; see **Figure 3B**).

The studies by Möller *et al.* have shown that drug delivery using pulsating aerosols is associated with slower clearance of the radiotracer from the nose compared with nasal pump spray delivery, suggesting penetration into the nose to sites with retarded mucociliary clearance, for example the anterior nasal cavity, olfactory epithelium, or the paranasal sinuses [26]. They concluded that clearance kinetics in the range of hours using pulsating aerosol delivery, compared with 10 – 20 min using nasal pump sprays, may provide longer residence times of a drug administered to the nose as pulsating aerosol, and may prevent rapid removal by mucociliary clearance and by circulation, therefore allowing formulations with sustained release profiles and possibly once daily application even with shorter half-time values.

3.2 Opportunities for the aerosol treatment of nasal disorders

Systemic and topical treatment in chronic rhinosinusitis is applied using antibiotics, antihistamines, steroids, saline and other drugs (i.e., decongestants) [1,34-39]. For topical treatment nasal lavages and nasal pump sprays are available, but because there is no drug delivery to the sinuses when using these techniques, treatment success is limited [40]. The limited success of topical treatment options is one reason for the high rate of functional endonasal sinus surgery (FESS). However, after surgery topical treatment options are needed, where nasal lavages (irrigation) and nasal pump sprays are used at present [24,41]. As there is a high rate of recurrence after FESS [3], FESS is repeated several times in some patients. Efficient topical treatment options are needed to provide a successful 'post-surgery treatment' strategy, and the low volume pulsating aerosol delivery method could fulfil this task.

The sinus aerosol deposition fraction of 6.5% is in the range of results obtained in the authors' previous *in vitro* studies using a nasal cast model, where up to 8% of the nebulized dose could be deposited in the paranasal sinuses [33]. Six-and-a-half per cent deposited dose in the sinuses may provide a sufficient amount of drug for a first step topical therapy. The mass output rate of the available pulsating aerosol devices (0.2 ml/min for the PARI Sinus and 0.3 ml/min for the PARI Vibrent) is in the range of nasal pump sprays (typically 0.1 ml/puff). For example, a 1-min delivery using the pulsating aerosol device would deposit amounts comparable to 2 puffs of a nasal pump spray in the nasal cavity and ~ 10 – 15 mg of nebulized solution in the sinuses (based on 70% deposition in the nasal cavity and 6.5% deposition in the sinuses).

Drug delivery to the sinuses using pulsating air flow was also confirmed in studies by Maniscalco and co-workers [11,42]. In these studies pulsation was induced during humming, and they could show release of nitric oxide (NO) from the sinuses and its suppression by inhalation of the nitric oxide-synthase inhibitor L-NAME; but these studies imply nasal inhalation, as humming can be performed only during exhalation. This protocol implies access of the drug to the lung. Although they reported reduction of NO release from the sinuses after nitric oxide-synthase inhibitor administration, they did not report efficiency data. In the case of using antibiotics or steroids, the pulsating aerosol treatment technique proposed by the PARI devices with closure of the soft palate prevents drug delivery to the lung and thereby reduces side effects, which are known from therapy of chronic lung diseases using such drugs. Closure of the soft palate is a requirement for efficient application of pulsating aerosol delivery. There may be limitations of compliance and acceptance by patients during long-term use, as known from most inhalation therapies [43]. Therefore, proper instruction and training is required before therapy starts in order to achieve optimal patient compliance.

As the sinuses are opened during FESS, there is an improved effectiveness of topical treatment using nasal irrigation, but drug delivery to the sinuses using nasal pump sprays is still limited. Using pulsating aerosols for topical sinus drug delivery after FESS may also be an interesting treatment option, because the larger ostia offer better access of an aerosol to the sinuses and increased deposition rates compared with the status before operation [44].

Patients with dysfunctions of the ciliary transport apparatus, such as PCD and CF patients, use daily inhalation of mucolytics and other drugs to enhance mucus transport out of the lung. As the disease also manifests in the upper airways and the patients suffer from CRS, topical treatment of the nasal cavity including the sinuses is required. Preliminary clinical data in CF patients are available after nasal administration of Dornase alpha (Pulmozyme) using pulsating airflow with improvements in the Sinonasal Outcome Test-20 (SNOT-20) [18,45]. The SNOT-20 is a

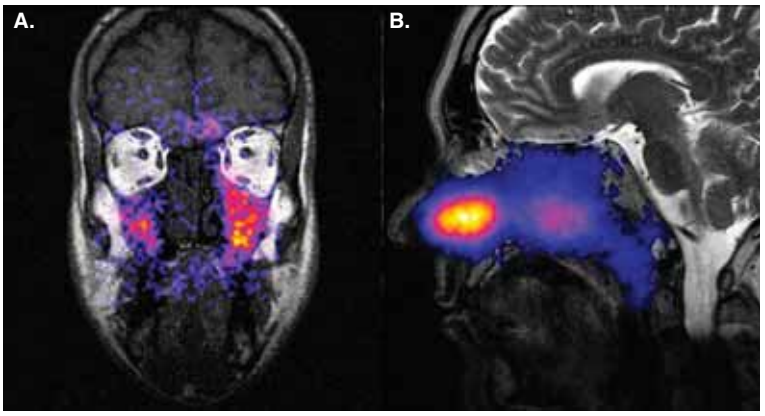

Figure 3. Superposition of anterior gamma camera images of ^{99m}Tc-DTPA aerosol deposition after pulsating airflow delivery with a coronal magnetic resonance tomography image in one subject (A) after shielding of the activity in the central nasal cavity, showing ^{99m}Tc-DTPA aerosol penetration into the maxillary and frontal sinuses. B. Lateral distribution of ^{99m}Tc-DTPA aerosol deposition showing activity access to the ethmoid and sphenoid sinuses.
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quality of life measure specific for patients with CRS symptoms, where psychological functions, sleep functions, rhinological symptoms, and ear and/or facial symptoms are assessed [46].

The available studies on pulsating aerosol application in nasal drug delivery are limited to healthy volunteers with normal nasal anatomy; therefore, the results may not directly be applicable to patients with CRS. Nasal obstructions in patients with rhinosinusitis and complete closure of ostia may prevent gas and aerosol penetration to the sinuses. However, the effectiveness of the system in patients suffering from CRS has to be shown in future clinical trials.

Declaration of interest

W Möller received a research grant from PARI GmbH, Starnberg, Germany, for testing nasal drug delivery devices. The other authors declare no conflicts of interest.

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