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 CRS. Chronic inflammation of the nasal mucosa results in trigger of defense reactions, mucosal swelling (including polyposis), increased mucus secretion, loss of cilia, airway obstruction and blocked sinus drainage. Under these conditions, bacteria and viruses may proliferate and cannot be removed from the nasal cavity and sinuses by normal ciliary function and clearance mechanisms. In addition, impaired mucociliary clearance in patients with primary ciliary dyskinesia (PCD) or cystic fibrosis (CF) also causes chronic sinusitis, and other chronic respiratory diseases, such as asthma and COPD, are linked to CRS.

Due to the limited therapeutic success of both oral and of topical treatment regimes, functional endonasal sinus surgery (FESS) has been the primary approach for treating CRS. An effective topical therapy is an unmet need and may allow new therapeutic options treating upper respiratory diseases prior to or post surgery.

The sinuses are poorly-ventilated hollow organs, making topical aerosol based treatments complex and difficult since nebulised drugs do not penetrate into these areas. However, gas and aerosol transport into non-actively ventilated areas can be achieved by diffusion and flow induction caused by pressure differences, and pulsating air-flows are generating such pressure gradients.

AEROSOL-BASED DRUG DELIVERY TO THE RESPIRATORY TRACT

Aerosolised drug delivery to the lower respiratory tract, either for topical or systemic therapy, has been used for a long time and is an established therapeutic concept using metered-dose inhalers (MDIs), dry-powder inhalers ( DPIs) and nebulisers. Although these devices were adapted for nasal drug delivery, their approval is limited to the treatment of nasal hayfever and allergic symptoms. The upper and lower airways exhibit many similarities since they are for instance ciliated and show mucus transport. Many upper and lower respiratory tract diseases are linked with each other supporting the concept of "united airways". For example, recent evidence suggests that allergic inflammation in the
upper and lower airways (asthma) co-exist, but their inter-relationship is poorly understood. In addition, chronic airway inflammation in CF patients is usually linked to the lower airways, but since mucus stiffening and mucus hyper secretion also occurs in the upper airways, CF patients suffer from CRS.\(^6\) However, differences in anatomy implies specific requirements of topical drug targeting, which can be achieved in part by selecting aerosol particle sizes and breathing patterns, and by specific nebuliser device configurations including different modes of administration.

PARI GmbH, Starnberg, Germany, has outstanding experience and reputation in the field of pulmonary drug administration by jet nebulisers. PARI Pharma, a separate entity, is focusing on novel drug formulations, such as liposomal cyclosporine A, complexation and taste masking of antibiotics, as well as on device concepts such as the eFlow nebuliser platform technology.\(^7,8\)

Recently, PARI Pharma has developed a pulsating aerosol drug delivery platform (PARI SINUS\(^TM\) and Vibrent\(^\circ\)) for the treatment of upper airway diseases by targeting drug delivery to the posterior part of the nose including the paranasal sinuses. The achievements obtained and future treatment perspectives are described in the following paragraphs.

**CURRENT NASAL DRUG DELIVERY SYSTEMS**

Standard medical nebulisers, such as jet nebulisers or vibrating membrane nebulisers, can be used for aerosol generation. 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) with an aerodynamic diameter below 5 \(\mu\)m.\(^9\) In addition, since the predominant deposition mechanism in the nose is impaction, the flow rate should be kept moderate.

One current topical treatment option of nasal disorders is the use of nasal pump sprays. These generate droplets between 50 \(\mu\)m and 100 \(\mu\)m diameter and volumes between 50 and 200 \(\mu\)l being administered by mechanical actuation in one nostril, each. Different drug formulations are available for use with nasal pump sprays, such as saline, decongestants, mucolytics or steroids. Although 100% of the administered drug deposits within the nose several studies have demonstrated that there is no significant aerosol access to the paranasal sinuses.\(^9,10\) To address this unmet need new nasal aerosol delivery devices are being developed, like the ViaNase (Kurve Technology Inc, Lynnwood, WA, the US) and the Optinose (OptiNose AS, Oslo, Norway). However, these do not use pulsating airflow techniques.\(^11,12\) These devices may be superior to nasal pump sprays and improve nasal drug delivery due to a smaller particle diameter of the aerosol and improved delivery techniques. Nevertheless, delivery of aerosol to the sinuses could not be proven and is unlikely since droplets or particles >10 \(\mu\)m can hardly travel and penetrate to the sinuses. This is supported by the limited ventilation of the sinuses and basic aerosol physics, as shown by investigations in a human nasal cast model and apparent from the operation conditions of these devices.\(^13,14\)

Nasal irrigation with isotonic or hypertonic saline is an inexpensive and essentially risk-free treatment and is widely used as a non-aerosol-based nasal rinse and drug delivery method.\(^15\) Although the overall fluid retention in the nose is very low, nasal irrigation with volumes of 20-250 ml via syringes, squeeze bottles and Neti pots have proven to be beneficial in removal of inflammatory cells and excess mucus, including wound cleaning after functional endoscopic sinus surgery (FESS).\(^16\) However, drug delivery to the sinuses using nasal irrigation of such solutions containing drugs may only be possible post sinus surgery,\(^16\) and lacks reproducible dosing and reliable treatment efficacy. Due to a lack of better alternatives, anti-inflammatory drugs, such as steroids were added to isotonic nasal rinse solutions and used as an anti-inflammatory treatment concept in CRS patients primarily post FESS.

**DISCOVERY OF PULSATING AIRFLOWS FOR SINUS DRUG DELIVERY**

The development of pulsating aerosols is based on discoveries by Hermann von Helmholtz, who found resonance conditions for gas exchange between secondary spaces (such as the sinus cavity) and the surrounding space.\(^17\) These devices were called Helmholtz resonators and were used for instrument tuning. Based on this knowledge early pulsating aerosol studies for sinus drug delivery were done in the last century by Guillerm and colleagues.\(^18\) Later Kauf systematically modeled and studied the penetration ability of aerosols into secondary spaces and performed first experiments on model cavities.\(^4\) These studies were continued by Hyo et al and Sato et al using nasal casts and human cadavers, and they also could confirm deposition efficiencies between one and four percent.\(^19\)

**PULSATING AEROSOL DELIVERY SYSTEMS**

A pulsating aerosol is an aerosol stream superimposed by a pulsating airflow. The first commercial pulsating aerosol delivery device was developed in France by La Diffusion Technique Francaise (Atomisor Automatic Manosonique Aerosol, DTF, Saint Etienne, France), which is based on the early Guillerm studies. In 2003, PARI GmbH, Starnberg, Germany, developed a commercial pulsating aerosol delivery device, the PARI SINUS, which has been approved in Europe via a CE marking.
The PARI SINUS is composed of a PARI LC STAR jet nebuliser with a mass median aerodynamic diameter (MMAD) of about 3 μm and a geometric standard deviation (GSD) of about 2.5. The output flow rate is 6 L/min, which is necessary to operate the nebuliser. A pulsation of 44 Hz is superimposed to the aerosol stream.

The PARI Vibrent is a more efficient electronic nebuliser utilising a customised perforated vibrating membrane as the aerosol generator (PARI eFlow) coupled with an adjustable pulsation (PARI Pharma GmbH, Starnberg, Germany). The Vibrent is able to generate droplets with a MMAD of about 3 μm and a flow rate of about 3 L/min causing less impaction. A flow pulsation at 25 Hz frequency is superimposed on the aerosol stream.

Figure 2: 99mTc-DTPA activity distribution image of a 100 μl metered pump spray (upper panel) versus the pulsating aerosol delivery for 20 seconds using the PARI Vibrent (lower panel) in lateral (A) and anterior view without a nasal shield (B) and with a nasal shield (C).

Administration of the pulsating aerosol is shown in Figure 1b. The Vibrent prototype handset is attached to one nostril and the nasal plug (flow resistor) in the other nostril. During delivery the subject is instructed to close the soft palate, which directs the aerosol from the delivery nostril to the output nostril, providing an aerosol pathway to the nasal airways only. Both, the output resistor and closing of the soft palate ensures optimal pressure transduction to the sinuses, inducing drug penetration to the paranasal cavities and prevents undesired lung deposition.

SINUS 99mTc-DTPA AEROSOL DEPOSITION AND CLEARANCE

For testing nasal and sinus aerosol deposition and clearance, a pulsating aerosol was generated using the PARI Vibrent as described above. In the studies by Möller et al, a solution composed of 99mTc-DTPA (diethylene triamine pentaacetic acid) was delivered to each nostril for 20 seconds, and deposition distribution was assessed by gamma camera imaging. The first image recorded immediately after aerosol delivery did not show aerosol deposition in the chest, confirming the tight closure of the soft palate during aerosol delivery.

Figure 2 shows anterior and lateral images of 99mTc-DTPA aerosol deposition distribution after nasal pump spray and after pulsating aerosol delivery (superimposed to coronal and sagittal magnetic resonance tomography (MRT) scans of the subject). With both delivery methods the dominant fraction was deposited in the central nasal cavity. After suppressing the central nasal cavity activity using a lead shield, the 99mTc-DTPA aerosol deposition in the maxillary sinuses clearly appears. There was 100% nasal drug deposition when using the nasal pump sprays and there was negligible drug penetration into osteomeatal area and the maxillary sinuses. With pulsating...
aerosol delivery total deposition in the nasal cavity (including sinuses) was 71 ±17 % of the nebulised dose and 6.5 ±2.3 % of the total nose activity penetrated to the sinuses.11,20

In addition, as shown in Figure 2, there is 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: 50 % of the dose was cleared after 1.2 ±0.5 hours and more than 20 % of the administered dose was retained in the nose after 6 hours (see Figure 3). The cumulative retained dose 6 hours after delivery was obtained from the area under the retention curve and corresponds to 1.98 ±0.23 normalised dose units.hr for the pulsating aerosol.11 Delayed clearance is of therapeutic advantage since drugs with a short half-life can be administered less frequently allowing a BID or once-daily dosing.

FIRST CLINICAL RESULTS

Case Studies Using the PARI SINUS and PARI Vibrent

Topical application of steroids using nasal pump sprays is a mainstay in allergic rhinitis and sinusitis therapy. There is evidence on polyposis that clinical symptoms are reduced when using intranasal steroids, but a complete cure can hardly be achieved, since the site and origin of inflammation is often located in the osteomeatal area and/or paranasal cavities. Two patients suffering from chronic polyposis CRS inhaled budesonide for a period of 6-12 weeks using the PARI SINUS or the PARI Vibrent. Figures 4 and 5 show anterior MRT images of the two subjects before and after the steroid treatment period. After the treatment period the blocked maxillary and ethmoidal sinuses were completely cured and showed normal appearance.

The CT images of another patient before and after inhaling budesonide via a PARI Vibrent prototype over six weeks is shown in Figure 5. The previously almost entirely blocked nasal passage was free and the inflammation of the ethmoid sinuses reduced.

In both cases surgical interventions could be prevented.

Experience in CF Patients

Patients with dysfunctions of the ciliary transport apparatus, such as PCD or cystic fibrosis (CF), inhale mucolytics and other drugs to enhance mucociliary clearance (MCC) to remove mucus from the airways. Since the disease also manifests in the upper airways, patients will benefit when administering such drugs into the nose and paranasal sinuses using pulsating aerosols.

Preliminary clinical data in CF patients demonstrate improvements in the Sinonasal Outcome Test-20 (SNOT-20) after nasal administration of Dornase alpha (Pulmozyme) using the PARI SINUS.12,21 The SNOT-20 is a quality of life measure (QoL) specific for patients with CRS symptoms, where psychological functions, sleep functions, rhinological symptoms, and ear and/or facial symptoms are assessed.22

Topical Treatment After FESS

Endoscopic sinus surgery (ESS) is an established method to improve ventilation of the paranasal cavities with the objectives that the innate immune system supported by medical treatment regimes will help to cure the disease. It is thought, that larger ostia may enable a better topical drug treatment.

To investigate this hypothesis, a subject who underwent ESS some years ago volunteered in a gamma scintigraphy deposition study. Surprisingly, no aerosol deposition could be detected in the paranasal cavities after administration of radiolabelled aerosol via a nasal pump spray whereas a deposition of about 0.4 % was found when a comparable tracer was administered via the PARI Vibrent, as clearly shown in Figures 6 and 7.

SUMMARY AND CONCLUSION

Ventilation of the target site is a significant requirement for aerosol drug delivery. It was shown that aerosols penetrated paranasal cavities only in such cases when a pulsation was applied, causing efficient sinus ventilation of radiolabeled 81mKrypton gas.23 In addition, pulsating airflow caused a sustained release of 81mKr-gas activity from the nasal cavity and the sinuses after switching off Kr-gas delivery.24
Furthermore, since aerosol was deposited in the ostia will be required to deliver drug into the sinuses. A substantial aerosol deposition of about 6.5% was only observed when aerosols were inhaled via Vibrer whereas paranasal deposition was below the detection limit upon administration of a radiolabeled aerosol via a nasal pump spray in 15 healthy volunteers.

The limited therapeutic success of topical treatments by nasal spray, irrigations and standard nebulised therapy may explain the high rate (about 500,000 annually in the US alone) of functional endonasal sinus surgeries (FESS). However, surgery does not usually effect a complete cure, but requires additional medicinal treatments, such as nasal irrigation with saline or saline with compounded drugs (such as steroids). Still, these treatment options are not very effective \(^{13,14}\) as is apparent from a high rate of recurrent FESS.\(^ {15}\)

Thus, there is an unmet need to improve topical treatment options pre- and post-surgery. Current data support our view that the Vibrer may offer new therapeutic perspectives as an efficient topical treatment option in CRS. However, clinical studies delivering inhaled steroids, antibiotics, mucolytics, antiviral or antifungal drugs to CRS sufferers are needed to demonstrate if this assumption can be verified. There is no doubt that open nasal airways and ostia will be required to deliver drug into the posterior part of the nose.

There is also hope that deposition characteristics and nasal aerosol distribution patterns seen in the deposition studies support the expectation that systemic delivery may be possible for drugs and formulations having a good permeability via the thin epithelium separating the posterior nasal surface from the highly vascularised tissue. Furthermore, since aerosol was deposited in the olfactory area, delivery to the brain including the central nervous system could be considered as novel treatment options.\(^ {16}\) Hence, the design of future clinical studies including selection of primary and secondary endpoints must address such issues to obtain more information better to understand drug absorption, systemic uptake, and potential drug delivery opportunities and perspectives.

REFERENCES