Introduction

Upper Airways and Sinuses

The nose and the paranasal sinuses constitute a collection of air-filled spaces within the anterior skull. The paranasal sinuses have a volume of about 5 to 30 milliliters and communicate with the nasal cavity through small apertures (figure 1). The ostium diameters range from about 0.5 to 17 mm (mean 1~3mm) with a large interindividual variability. Surface areas of the nasal and paranasal cavities are roughly 120 cm$^2$ and 180 cm$^2$ respectively. This is approximately the ten thousandth part of the lung surface area.

Chronic Rhinosinusitis: Prevalence & Current Treatment Options

The wide variations of definitions of chronic rhinosinusitis (CRS) make it difficult to accurately determine its prevalence. It can be assumed however that about 10 to 15% of the European and US population suffer from CRS$^{1,2}$. Rhinosinusitis is generally defined as an inflammation of the nose and the paranasal sinuses which is characterised by at least one of two cardinal symptoms: nasal obstruction or nasal discharge. They are associated typically with facial pain or pressure and a reduction or loss of smell. In some patients an underlying ciliary dysfunction is responsible for the development of a CRS. This holds true for cystic fibrosis (CF) and primary ciliary dyskinesia (PCD). For an exact diagnosis CT scans are very helpful as they depict, if and to what extent the normally airfilled spaces are plugged with mucus (figure 2).

Current therapy options of CRS are the administration of oral antibiotics or steroids, topical steroids and saline in the form of nasal sprays—or as a last resort—endonasal sinus surgery (ESS, FESS). Whereas the oral drugs provide at least limited access to the sinuses via general blood circulation, no access at all is possible with topical nasal sprays. The oral route, however, is associated with considerable systemic side effects. That is the main reason why a topical therapy is clearly desirable. Despite aggressive therapy there is altogether a discouragingly high recurrence rate of about 80%.

Challenges in Paranasal Sinus Aerosol Therapy

There are two main challenges that must be met to efficiently deposit aerosolised drugs within the sinuses:

- Aerosol droplets must be small enough to travel through the small ostia.
- Under normal circumstances the paranasal sinuses are not ventilated—a normal air flow from a conventional nebuliser or a spray will hence

Targeted Treatment for the Sinus Cavities

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Figure 1 Overview of the nasal and paranasal cavities (courtesy of Astra Pharmaceuticals).
just pass by the ostia and not enter the sinus cavities, irrespective of droplet size.

Whereas it is relatively easy to overcome the problem of suitable particle size of about 2–5 μm, the ventilation of the sinuses poses a central challenge. Two aspects have to be considered: the exposure time of the aerosol within the cavities should be maximized and a driving force that shoves the droplets from the nose into the sinuses should be created.

Both principles have been realised in the PARI SINUS device (figure 3): As the aerosol is introduced into the nose via one nostril, the second nostril is equipped with a flow resistor and the soft palate must be closed. Thus a confined space is created where the aerosol is maintained and exposure time is increased. The pathway that a liquid or an aerosol then takes through the nose can be easily understood when looking at a nasal shower (figure 4). The flow resistor inserted into the exit nostril leads to an effective pressure transmission to the nasal cavities. If additionally pulsating compressed air is delivered through the entrance nostril, a pressure fluctuation within the nasal and paranasal cavities is created, that forces the drug droplets into the sinuses (figure 5).

Study Data

Proof of Concept and Deposition Data

Data from different proof of principle studies is now available. Möller et al. could show already in 2007 that the principle of a superimposed pulsating air stream—which is realised in the PARI SINUS device—leads to a significant ventilation of the paranasal cavities whereas with constant airflow they are simply passed by. It was a study with radiolabeled "Krypton gas in three healthy volunteers and the extent of ventilation occurring through the ostia into the sinuses was made visible by gamma camera.
imaging for continuous as well as for pulsating flow (figure 6).

As a next step a drug solution was used instead of Krypton gas where drug deposition behaviour could be evaluated. Schuschnig et al. worked with a nasal cast model and Pulmozyme to evaluate the different deposition patterns of a nasal pump spray compared to the PARI SINUS device\(^7\). Pulmozyme as an inhaled mucolytic drug is especially used in cystic fibrosis and was thought useful also to help mucus clearance in the upper airways in this group of patients. The results were strikingly different: Whereas in vitro nasal deposition was acceptable for the pump spray, the device resulted in almost no drug deposition within the paranasal cavities. This was in contrast to the PARI SINUS which provided therapeutically relevant doses also to the model sinuses (table 1).

These results were confirmed in 2008 by a Japanese workgroup\(^8\). They found higher drug deposition in a sinus maxillaris model when drug was administered as a pulsating compared to a non-pulsating aerosol. Experiments were carried out with PARI SINUS within an in vitro nasal model. As a second step they measured drug deposition in the paranasal cavities in vivo in patients that had undergone prior sinus surgery. A comparison of their data for sinus deposition with data from an older

\(^7\)Targeted Treatment for the Sinus Cavities

\(^8\)
study showed significant superiority of the PARI SINUS. For the existing data of the prior study drug had been nebulised with an ultrasonic device. The authors concluded that the best in vitro results for drug transfer were achieved by inhalation using a pulsating aerosol with a simulated closed soft palate. They also found an excellent drug transfer in vivo to human sinus cavities with PARI SINUS.

**Clinical Data**

First clinical data are now available for the PARI SINUS device in allergic and chronic rhinosinusitis and cystic fibrosis patients. Geppe et al. found that PARI SINUS offered a non-invasive, painless rhinosinusitis therapy for children and preschool children. One week of therapy with the SINUS device had reduced the symptom burden in the young patients with allergic and viral rhinosinusitis more efficiently than a standard therapy regimen and had been well tolerated (figure 7).

Delivery of dornase alfa using a pulsating aerosol has also shown potential as treatment for cystic fibrosis related chronic rhinosinusitis. CRS is very common in cystic fibrosis patients. There is now increasing evidence that this upper airway disease may play a role as a source of lung infection with P. aeruginosa and should hence be consistently treated. Mainz et al. found significant improvement of the sino–nasal–outcome–test 20 (SNOT 20) and increased quality of life within a group of 23 cystic fibrosis patients. They had been suffering from concomitant CRS and they had administered dornase alfa for four weeks via PARI SINUS. The initiators of this study concluded that the new therapeutic concept of sinonasal inhalation with vibrating aerosols of PARI SINUS presents a promising treatment option. These results warrant further evaluation in larger cohorts.

A Japanese workgroup reported about positive experiences with PARI SINUS in sinusitis. They had treated 56 patients of all age groups with the pulsating aerosol and asked them to fill in a questionnaire on their subjective impression of this therapy. 75% of the patients claimed that they had felt positive effects, 80% reported a significant improvement in symptoms compared to a conventional nebuliser system and consequently 78% of the participants stated that they would favour PARI SINUS over other devices for future therapy.

**Conclusions**

Topical therapy of the paranasal sinuses is challenging. Under normal circumstances they are not ventilated and the narrow ostia represent a significant barrier for access of drug particles. A method of application is hence needed that provides the drug in droplets small enough to fit through the small openings as well as the pressure gradient that forces those droplets on their way into the cavities.

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**Table 1** Nasal Spray provides acceptable nasal deposition but almost no drug deposition within the paranasal cavities.

<table>
<thead>
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<th>Component</th>
<th>Pumpspray</th>
<th>PARI VibrENT/PARI SINUS</th>
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<tr>
<td>Nose</td>
<td>193 µg</td>
<td>28, 4–66, 8 µg</td>
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<tr>
<td>Paranasal cavities</td>
<td>0, 9 µg</td>
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Figure 7  One week of therapy with PARI SINUS reduced symptom scores in children with rhinitis more efficiently compared to a standard therapy regimen.

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Both principles have been realized for the PARI SINUS device. It delivers a pulsating aerosol with a high fine particle fraction. There is now much data proving that this principle of function is effective and leads to deposition of therapeutically relevant doses within the sinuses. This was shown with different in vitro models but also in vivo drug deposition data are available. First clinical data confirm that the PARI SINUS system offers a non-invasive, painless and well-tolerated treatment option allowing for an efficient therapy for sinunasal disease.

Further investigation is clearly warranted with larger patient groups. Several studies and evaluations are now ongoing and further results will follow.

References