PARI Respiratory Equipment, Inc.
White Paper

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Pulsating Aerosols Prove Highly Effective in Delivering Medications to the Sinuses

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New method overcomes limitations of inhaled drug deposition to the sinuses

Abstract

The PARI SINUS™ is an inhalation device that is designed to target drug delivery to the sinus cavities using a novel pulsating airflow technology. The paranasal sinuses are non-ventilated organs which, until now, have been difficult to deliver prescribed medication using conventional aerosol delivery systems.

The PARI SINUS pulsating aerosol delivery system has proven to be significant in delivering medications to the paranasal sinuses resulting in the reduction of sinonasal symptoms such as sinusitis and chronic rhinosinusitis (CRS) [(1)]. CRS, the inflammation of the nasal passages and sinus cavities is one of the most prevalent chronic illnesses in the US affecting persons in all age groups. Without proper treatment, CRS can lead to the total obstruction of the nasal passage due to chronic inflammation, infection and the excessive proliferation of polyps [(2)].

In clinical testing the delivery of dornase alpha via the PARI SINUS led to the significant reduction of sinonasal symptoms in CF patients with CRS [(3)]. The PARI SINUS was approved via CE marking process in Europe and most recently in the US via a 510(k) clearance.

Background

There is a high incidence of nasal disorders, including CRS, affecting about 14% of the total population. CRS can diminish quality of life and cause lost productivity. The predisposing factors for CRS are rhinitis, viral infections, allergy, gastroesophogeal reflux disease (GERD) and cystic fibrosis (CF). Existing topical treatment regimens

show only limited efficacy due to negligible drug delivery to the paranasal sinuses. Nevertheless, the primary treatment option of CRS is a combination of topical or systemic steroids, antibiotics and functional endoscopic sinus surgery (FESS).

Nearly all patients with CF have nasal and paranasal sinus disease. CF is a chronic, hereditary disease that affects the lungs and digestive system of about 30,000 children and adults in the United States. In 90 percent of CF cases, thick, sticky mucus forms in the lungs causing blockage of the airways, making it difficult to breathe and leading to serious lung damage and infections.

Over the course of the past two decades, the concept of inflammation involving both the upper and lower airways has become increasingly recognized and studied. Referred to as the "Unified Airway Theory", it asserts that a functional relationship or link between the upper and lower respiratory tract exists. The upper respiratory tract consisting of the nose and paranasal sinuses have the same mucosal lining as the lower respiratory tract or lungs. This concept may explain the possible role of sinus infections on the lower respiratory tract and the association of CRS in CF and rhinitis in asthma [(6)]. Clinical and epidemiological studies have shown that treatment to one area of the respiratory tract can have significant benefit to the entire system [(7).]

Considering the high incidence of CRS, it was recognized early on that delivering medication to the paranasal sinuses would be beneficial particularly for those with CRS (Fig. 1).

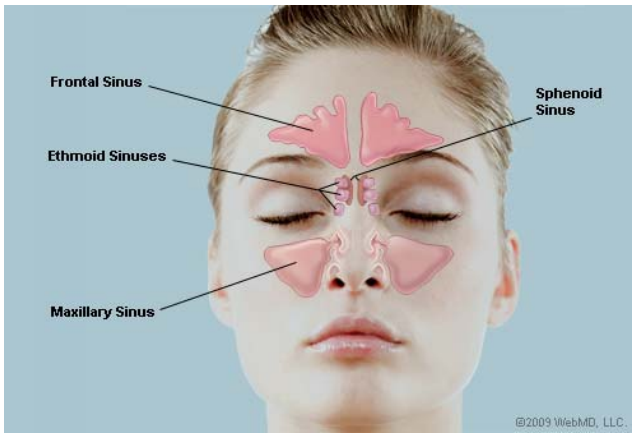

Fig 1. *The paranasal sinuses are cavities in the interior of the maxilla, frontal, spheroid and ethmoid bones. The sinuses develop as outgrowths from the nasal cavity; hence they all drain directly or indirectly into the nose.*

However, such treatment was found to be substantially limited in that the paranasal sinuses are air-filled hollow cavities (organs) located in the bones of the skull surrounding the nose. These cavities are accessible only through a single passageway, the ostium. As a result, conventional aerosol delivery systems are virtually ineffective for such applications. It was the subsequent development of a delivery system utilizing a pulsating aerosol flow that proved to be the most efficient strategy to deliver medication to each of the six paranasal sinus cavities (Fig 2).

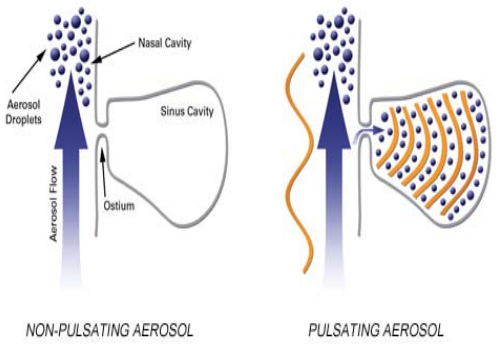

Fig 2. *Pulsating airflow creates an oscillating pressure differential between the main nasal cavity and the sinuses enabling an aerosol stream to reach the closed cavities of the sinuses.*

The first commercial pulsating aerosol delivery device was developed in France by La Diffusion Technique Francaise (Atomisor Automatic Manosonique Aerosol, DTF, Saint Etiene, France). In 2003, PARI GmbH, (Starnberg, Germany), developed a commercial pulsating aerosol delivery device which has evolved to the present day PARI SINUS product.

How it Works

The PARI SINUS pulsating aerosol delivery system (Fig 3) is comprised of the PARI SINUS compressor that superimposes a pulsating airflow onto a standard PARI SINUS nebulizer. The compressor includes an integrated pressure wave generator driven by the same motor. The output pressure wave is coupled via tubing connected to the top of a PARI SINUS jet nebulizer which superimposes the pressure wave onto the aerosol flow.

This combination delivers a pulsating aerosol stream with droplets sizes having a mass median aerodynamic diameter (MMAD) of 3 microns (µm) and geometric standard deviation (GSD) of 2.5um [(4).] The output flow rate for this device is 6 liters per minute with a pulsation frequency of 44.5 Hz.

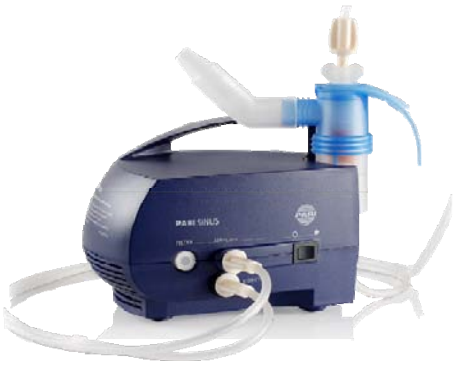

Fig 3. *PARI SINUS system including compressor with pulsating air flow and standard PARI SINUS Nebulizer* (*courtesy of PARI).*

The patient/nebulizer interface is connected to one nostril via a nasal adapter insuring an air-tight fit (Fig.4). A flow resistor is attached to the other nostril. For effective transmission of the pulsating aerosol, the patient closes the soft palate while receiving the softly pressurized air flow through one nostril and releasing it through the other.

Fig 4. Sinonasal *inhalation with PARI SINUS pulsating aerosol delivery system (courtesy of PARI).*

Standard nebulizers, such as jet or vibrating mesh nebulizers approved for delivery to the lower respiratory tract are used routinely for aerosol delivery to the nasal and paranasal cavities. However, 100% of the administered drug may deposit in the nose with these nebulizer types, several studies have demonstrated that the individual droplets generated by these devices are of sizes far too large to gain access to the paranasal sinuses. For effective medication delivery to the sinuses, a pulsating aerosol stream with uniform droplet sizes with an MMAD of 3 -5 µm is needed. To minimize impaction in the nose, it is important that a moderate flow rate be maintained.

Clinical Studies

Proof of Concept studies were performed in healthy volunteers to confirm ventilation and deposition with a pulsating aerosol in human sinus cavities. The ventilation patterns created by aerosol flows, without and with pulsation respectively, are superimposed on the test subject's MRI images (Fig. 5). The image on the left shows the areas (in red) that are ventilated during inhalation without pulsating airflow. Only the main nasal cavity is reached. The image on the right illustrates the active principle of the PARI Sinus pulsating airflow.

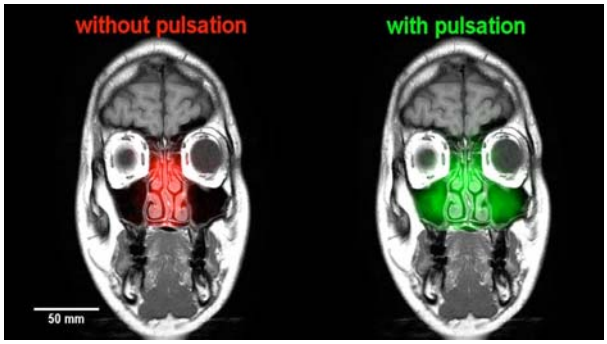

Fig 5. *Lateral MRI slice showing marker gas distribution without pulsation (left image) and with pulsation (right image0 within the nasal cavity and the maxillary sinuses (courtesy of PARI).*

Compared to aerosol administration with conventional nasal pump sprays, it has been shown that 99mTc-DTPA aerosol deposition in the paranasal sinus cavities was significantly higher with the PARI SINUS (4.2 ± 0.3 %) compared to the nasal pump spray (<1%). Further, 50% of the medication was cleared after 1.2 ±0.5 hours and more than 20% of the delivered dose was retained in the nose after 6 hours with the PARI SINUS (Fig. 6). The cumulative retained dose 6 hours after delivery was obtained from the area under the retention curve (AUC). Delayed clearance is a therapeutic advantage since drugs with a short half-life can be administered less frequently allowing a once or twice daily dosing.

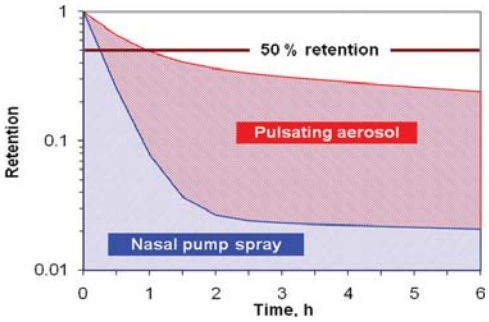

Fig 6. *Nasal retention during six hours in one volunteer after delivery using a nasal pump spray or the pulsating aerosol device (with permission from American Academy of Otolaryngology – Head and Neck Surgery Foundation)*

A case study in a patient with chronic polyposis CRS scheduled for sinus surgery, nasally inhaled 1 mg budesonide once daily for 12 weeks with the PARI SINUS using the standard protocol with closed soft palate. MRI was done before and after the treatment period. After therapy with PARI SINUS the CRS-patient's symptoms improved. Blockages of maxillary and ethmoid sinuses were resolved and surgery was avoided [8] (Figure 7).

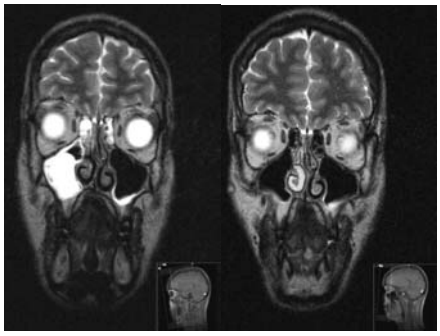

Fig. 7. *Coronal MRI (T2 weighted) slice of a patient before (left) and after (right) a three month once daily treatment with steroids (budesonide) using the PARI SINUS pulsating aerosol device*.

Looking Forward

To expand on the findings of earlier studies, several on-going clinical studies are being conducted in CF and CRS with the PARI SINUS device. Various drugs are being studied including antibiotics, anti-inflammatory, and hypertonic saline solution. Study endpoints include quality of life measures specific to CRS sufferers using the Sinonasal Outcome Test-20 (SNOT-20), MRI imaging, bacterial eradication and avoidance of surgery [5]. At a recent medical conference, results were presented from a multi-center placebo controlled study using the PARI SINUS device to deliver tobramycin in CF patients with CRS. Results demonstrated that those patients administered tobramycin via the PARI SINUS had significant improvement in quality of life compared to those patients in the placebo group. A future PARI SINUS study delivering an anti-inflammatory in CRS patients is planned.

With more than 20 publications representing both in-vitro work and clinical studies on the PARI SINUS, data demonstrate that sinus drug therapy is possible when a pulsating aerosol delivery system is used. The PARI SINUS offers new therapeutic options for CRS sufferers. Recent studies show that drug delivery via pulsating aerosol can improve quality of life. Additional studies are warranted to determine if this new treatment modality may help delay or avoid more costly treatments or surgeries, such as FESS or serve as an adjunct therapy to those having recent sinus surgery.

Notes

(1) “Rhinosinusitis” is a newer classification of sinusitis where it takes into account that inflammation of the sinuses cannot occur without some inflammation of the nose as well (rhinitis).

(2) Nasal polyps are a non-cancerous mass of tissue inside the nose. The nose is lined with a layer of tissue called mucosa, and nasal polyps occur when this tissue becomes inflamed due to a variety of illnesses. Nasal polyps can be caused by allergies, asthma, allergic rhinitis, cystic fibrosis and other disorders of the nose and sinuses.

(3) Dornase alfa (proprietary name Pulmozyme from Genentech) is a highly purified solution of recombinant human deoxyribonuclease I (rhDNase), an enzyme which selectively cleaves DNA. Dornase alfa hydrolyzes the DNA present in sputum/mucus of cystic fibrosis patients and reduces viscosity in the lungs, promoting improved clearance of secretions.

(4) MMAD (or MMD) - Mass Median Aerodynamic Diameter or Mass Median Diameter.
Mass is used to describe a polydisperse aerosol such as that produced by most aerosol-generating devices used in clinical practice. MMAD is the particle size above and below which 50% of the mass of the particles is contained. The higher the MMAD, the more particles are of larger diameters.

(5) The Sinonasal Outcome test 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.

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