DRUG DELIVERY TO THE SINUSES VIA PULSATING AEROSOLS - RESULTS FROM A SCINTIGRAPHIC DEPOSITION STUDY IN HEALTHY VOLUNTEERS

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Introduction

- There is limited success in topical drug delivery to the nose and the paranasal cavities despite the high incidence of nasal disorders and the unmet need in the treatment of chronic rhinosinusitis (CRS) [1, 2].
- Recent studies in CF patients demonstrate that the upper airways are colonized with bacteria of the same genotypes as found in the lower airways, underlining the necessity of a concomitant treatment of upper and lower airways [3].
- Although the sinuses are virtually non-ventilated hollow organs, it is possible to ventilate the sinus cavities by generating pulsating air flows [4, 5].
- The objective of this study was to visualize sinus ventilation in 15 healthy human volunteers using dynamic 81mKr-gas ventilation imaging in combination with the Vibrent pulsating drug delivery system.
- In addition aerosolized drug delivery efficiency, clearance and systemic translocation was studied using 99mTc-DTPA aerosol.

Materials and Methods

- **Device:** The pulsating aerosol was generated by the PARI Vibrent pulsating drug delivery device generating the aerosol via a perforated vibrating membrane (Figure 1 and Table 1) developed by PARI Pharma GmbH, Starnberg, Germany.
- **Ventilation:** A 81mKr-gas generator was coupled to the Vibrent compressor inlet.
- **Aerosol delivery:** The nebulizer was loaded with 4 ml of 99mTc-DTPA and the pulsated aerosol administered for 20 sec in both the left and right nostril.
- **Planar gamma camera imaging** was applied to measure radiolabeled drug deposition and distribution directly after aerosol administration and 24 h after the treatment to assess retention and 99mTc-urine excretion.

**Nebulizer:** Vibrent
- Particle size: 3.0 µm MMD, GSD = 1.5
- Aerosol flow rate: 3 lpm
- Pulsation frequency: 25 Hz
- Aerosol output: 300 mg/min

**Table 1: Performance characteristics of the PARI Vibrent pulsating aerosol delivery device**

<table>
<thead>
<tr>
<th>Nebulizer: Vibrent</th>
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**Results of 81mKr Gas Ventilation**

**Figure 3:** Central nasal cavity lead shield and imaging in front of the gamma camera.

**Results of 99mTc Labeled Aerosol Deposition**

**Figure 4:** Superposition of 81mKr-gas gamma camera images with MRI scan without (A) and with (B) pulsating gas delivery

**Table 2:** 50 % retention

<table>
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<tr>
<th>Nasal pump spray</th>
<th>PARI Vibrant</th>
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<tr>
<td>50 % nasal retention</td>
<td>14 +/-3.4 min</td>
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<tr>
<td>24 h nasal retention</td>
<td>2.4 +/-1.8 %</td>
</tr>
<tr>
<td>6 h cumulative dose</td>
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**Figure 6 & Table 3:** Clearance kinetics and cumulative dose during 6 h after application

**Summary and Conclusions**

- Ventilation of the osteomeatal area and paranasal sinuses can only be achieved with a pulsating aerosol delivery system, but not with a constant flow system, such as a nasal pump spray or jet nebulizer.
- Between 4 and 10 % (mean 7.1 +/-1.4 %) of the nebulized dose could be deposited into the sinus cavities when the Vibrent pulsating aerosol system was used.
- An about 5-fold higher residence time of the deposited drug may be achievable for pulsating aerosol delivery in comparison to nasal sprays (t1/2 ~ 1.2h vs. 14 min) [2].
- Data strongly indicate that aerosolized sinus drug therapy is possible when a pulsating aerosol delivery system is used.
- Pulsating aerosol is further investigated in an on-going deposition study with CRS patients.

**References**


Figure 2: Left: Anterior gamma camera imaging of 81mKr-gas ventilation in a human volunteer. Right: Nasal 99mTc-DTPA pulsating aerosol delivery in a volunteer.

Figure 3: Central nasal cavity lead shield and imaging in front of the gamma camera.

Figure 4: Superposition of 81mKr-gas gamma camera images with MRI scan without (A) and with (B) pulsating gas delivery.

Figure 5: 99mTc-DTPA activity distribution image of a 100 µl metered pump spray (upper panel vs. the Vibrent delivering for 20 seconds about 100 µl as a pulsating aerosol (lower panel) in lateral (A) and anterior view without a nasal shield (B) and with a nasal shield (C ).

Figure 6 & Table 3: Clearance kinetics and cumulative dose during 6 h after application.

**Table 2:** % radioactivity distribution (n=15) regarding total, sinus and lung deposition

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<tr>
<th>Nasal pump spray</th>
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<tr>
<td>Total aerosol deposition: 100%</td>
<td>71 +/-17 %</td>
</tr>
<tr>
<td>Sinus aerosol deposition: &lt; 1 %</td>
<td>7.1 +/-1.4 %</td>
</tr>
<tr>
<td>Lung deposition, % output</td>
<td>0 0</td>
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