Paranasal aerosol delivery of Budesonide using PARI VibENT

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Introduction

- Nasal sprays containing corticosteroids are widely used for the treatment of chronic and allergic sinusitis even though the coarse spray deposits mainly at the nasal valve and is unable to reach the posterior nasal region [1,2].
- The pulsating aerosol device PARI SINUS™ (Figure 1) ventilates [3] and delivers aerosol to the sinuses [4]. Results from a clinical trial in CF patients are also very promising [5].
- PARI VibENT™ is a novel device (Figure 2) that combines a vibrating mesh aerosol generator with PARI SINUS pulsating action.
- CBIS is a novel aqueous inhalation formulation utilizing sulfobutylether-7-5-cyclodextrin (Captisol®) to solubilize budesonide.

This study was undertaken to:
- assess the drug distribution pattern of CBIS in a nasal cast model (NC) using a PARI VibENT prototype and
- investigate the effects of sinus volume and ostium diameter on delivery efficiency.

Materials and Methods

- Nebulization efficiency was investigated using a novel human cast deposition model developed by PARI (Figures 3,4,5). This cast model is based on anatomical dimensions and is equipped with bilateral cavities (sinuses) in the frontal, maxillary and sphenoid positions. Cavities as well as ducts are exchangeable, allowing variation of the sinus volume and duct diameter (Figures 3,4,5).
- A design of experiments was used varying the sinus volume (SV) on 4 levels (4, 7, 12 and 23 mL) and the ostium diameter (OD) on five levels (0.6, 1, 2, 3 and 6 mm). Ten randomized experiments, resulting in 60 sinus/ostium combinations, were carried out.
- After nebulization the cast model was dismantled and drug extracted from the paranasal cavities including the ducts and the nasal cavity, as well as from the nebulizer and the filter.
- Budesonide contents were assayed by a HPLC UV method developed in PARI Pharma’s laboratories.
- The aerosol’s mass median diameter (MMD) of 3.7 µm was measured with a pressure transducer (Malvern Spraytec, Herrenberg, Germany).
- Mean deposition in a single sinus cavity was 2.6% ± 0.28% (mean ± sd, n=50) of the initial charge dose at a sinus volume of 12.5 mL SV and ostium diameter of 2.8 mm.
- The mean total sinus deposition was 15.9%, 57.7% was measured from the nasal cavity, 15.2% was expelled, and 2.1% remained in the nebulizer.
- Deposition in the single sinuses ranged from 0.1% up to 7% depending on sinus volume (p<0.001) and ostium diameter (OD p=0.045, OD² p=0.004).

The deposition increases with increasing sinus volume (Figures 6 & 7).

- Highest deposition was observed in the range from 1.5 to 3.5 mm OD while deposition efficiency decreases at an OD < 1mm and at 6 mm (Figures 6 & 7).
- Mean sinus deposition at 0.6 mm OD was higher than with 6 mm OD (1.2 ± 0.3% LC vs. 0.7 ± 0.6% LC, n=14). The lowest sinus deposition was found for 6 mm OD and 4 mL SV (0.3 ± 0.1% LC, n=3).

Results

- It is possible to deliver budesonide aerosol to the sinuses via pressure pulsations.
- Interestingly, sinus deposition with very narrow ostia (0.6 mm) is higher than with wide ostia (6 mm).
- These results indicate that the PARI VibENT might be a conservative therapy option prior to surgery.

Conclusions

- Nebulization efficiency was investigated using a novel human cast deposition model developed by PARI (Figures 3,4,5). This cast model is based on anatomical dimensions and is equipped with bilateral cavities (sinuses) in the frontal, maxillary and sphenoid positions. Cavities as well as ducts are exchangeable, allowing variation of the sinus volume and duct diameter (Figures 3,4,5).
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- The aerosol’s mass median diameter (MMD) of 3.7 µm was measured by laser diffraction (Malvern Spraytec, Herrenberg, Germany).

Figure 1: 81mKr-gas distribution without (w/o slice, showing the nasal cavity and the maxillary sinuses.
Figure 2: VibENT prototype nebulizer: using the vibrating mesh aerosol generator.
Figure 3: Top view of the experimental set-up: The aerosol is carried by a continuous air flow (5) from one nostril through the nasal cavity and is retained on an exit filter at the exit nostril which is fit with a flow resistor (1). The pressure fluctuations (2) are coupled into the model from the opponent nostril. The resulting pressure amplitude is measured with a pressure transducer (3) inside the model.
Figure 4: Right half of the nasal cast model with three disassembled ducts.
Figure 5: Nasal cast with VibENT prototype.

Literature