

In-vitro Study of Aerosolised Colistin Delivered to the Nasal Tract via a Pulsating Aerosol Delivery Device (Vibrent®)

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Introduction

- Vibrent® is a novel investigational device to deliver aerosolised drugs to the paranasal sinus cavities and the posterior osteomeatal regions of the nose. These areas are frequently involved in chronic rhinosinusitis, but are hardly reached by conventional topical nasal medications.
- Successful aerosol delivery to the sinus cavities of healthy volunteers and chronic sinusitis patients has been demonstrated in previous deposition studies [1,2] using a Vibrent prototype.
- Inhaled colistin is widely used for the treatment of pseudomonas aeruginosa infections in the lower respiratory tract of CF patients. Recent publications [3,4] demonstrate that the upper airways are often colonised with bacteria of the same genotype as the lower airways. Hence, a comprehensive treatment of upper and lower airways is desirable.
- For subsequent clinical trials the Vibrent prototypes were re-designed to comply with the latest CE requirements.
- This in-vitro study was conducted to characterise the new clinical devices and to estimate colistin amounts delivered to the nose and the sinuses.

Materials and Methods

- For the experiments 1 ml isotonic NaCl inhalation solution was added to one ampoule of ColiFin® 1 MIU (PARI Pharma, Starnberg) and left, for about five minutes, until the powder was completely dissolved. Then, the ampoule was gently agitated and filled into the investigational Vibrent handset.
- Aerosol droplet size as Mass Median Diameter (MMD) was assessed by laser diffraction in comparison to isotonic saline. The Total Output Rate (TOR) was determined gravimetrically.
- The deposition study was conducted in a human nasal cast (Fig. 4, 5) equipped with 6 variable glass bottles and variable inserts mimicking the ostia. In this study, the model was configured with the following sinus volumes and ostium diameters: Frontal sinuses (FL, FR): 7ml / 1mm; Maxillary sinuses (MR, ML): 23ml / 2mm; Sphenoid sinuses (SR, SL): 12ml / 6mm. The length of all ostia was 9 mm.
- 1ml of colistin (80mg/mL) was aerosolised with the Vibrent for 2.5 minutes into each nostril of the model, while the opposite nostril was equipped with a flow resistor and a filter to capture the expelled drug. Since the model mimics the soft palate being closed, the aerosol is passing from the inlet nostril through the nasal cavity and exiting the model through the other nostril.
- At the end of the experiment the model was dismantled and drug was extracted with solvent from the ostia, the sinuses and the nasal cavity. The drug on the filter and the nebuliser residue were also recovered.
- The colistin assay of these solutions was determined by HPLC. The displayed results are the mean values of 6 experiments (2 devices, n=3) expressed as percent age of the label claim (80mg).

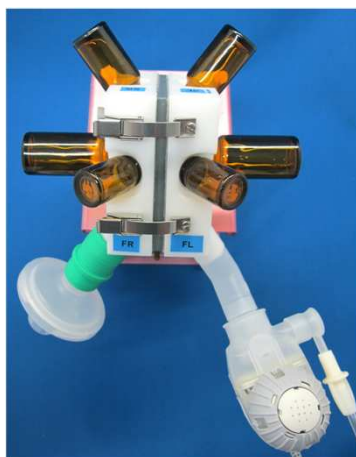


Figure 1: Top view of the cast model with Vibrent handset connected to the left nostril and the filter at the right nostril

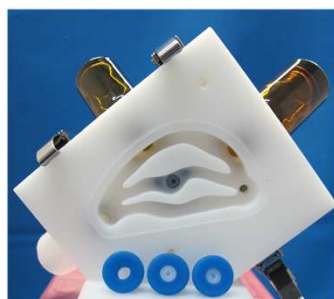


Figure 2: right half of the cast with three disassembled ostia with 6, 1 and 2 mm diameter.

Results

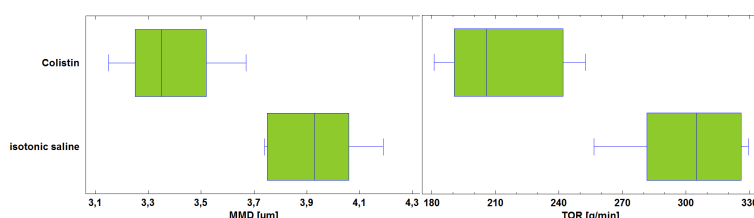


Figure 3: Mass Median Diameter (MMD) and Total Output Rate (TOR) of nebulised Colistin versus isotonic saline

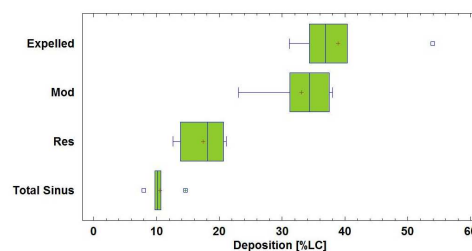


Figure 4: Distribution of colistin expressed as % of label claim [%LC] at the end of experiment on exit filter (Expelled), nasal cavity (Mod), handset (Res) and the sum of all six sinuses (Total Sinus)

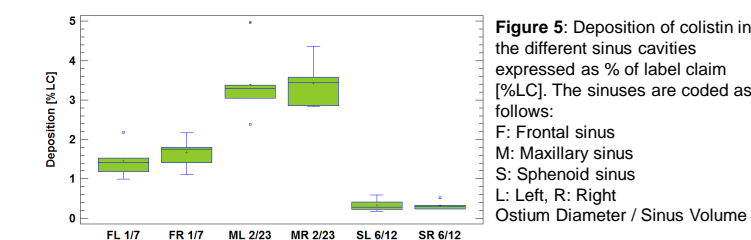


Figure 5: Deposition of colistin in the different sinus cavities expressed as % of label claim [%LC]. The sinuses are coded as follows:
F: Frontal sinus
M: Maxillary sinus
S: Sphenoid sinus
L: Left, R: Right
Ostium Diameter / Sinus Volume

- Compared to saline, colistin (80mg/ml) has a smaller droplet size (MMD 3.4 vs. 3.9 µm, p<0.01) and lower TOR (213 vs. 301 mg/min, p<0.01) (Fig.3)
- After nebulisation 11% of the colistin charged dose was found in all six sinus cavities (Fig. 4).
- In-vitro deposition in the single sinus cavities ranged from 0.3% to 3.3% depending on sinus volume (7-23 ml) and ostium diameter (1-6 mm) (Fig.5)
- 17% of the initial drug charge remained in the nebulizer while 33% were found in the nasal cavity and 39% were found on the filter. (Fig.4)

Summary and Conclusions

- 1MIU ColiFin® can be dissolved in 1 ml saline and delivered to the upper respiratory tract with the Vibrent aerosol delivery device (PARI) within 5 minutes.
- Interestingly, the largest ostia with 6 mm diameter yielded the lowest deposition which is in accordance with earlier findings [5].
- These data are comparable to earlier in-vivo deposition data in healthy volunteers (11% vs. 8% total sinus deposition, 33%vs. 46% nasal cavity deposition and 39% vs. 29% on exit filter) [2]

References

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