Drug Delivery to the Sinuses - Basics and Aerosol Dynamics

Uwe Schuschnig, Axel Krüner, Elisabeth Kloper, Norm Tiffin, Ashley Weigand, Martin Luber, Manfred Keller
PARI Pharma GmbH, Munich, Germany
Contact: u.schuschnig@pari.de (www.paripharma.com)

Introduction

The paranasal cavities and the posterior regions of the nasopharynx are poorly accessed with current topical drug delivery systems [1,2]. The idea of aerosol transport into the sinuses via “vibrating” or “sonic” aerosols suggests that pressure fluctuations increase aerosol diffusion and ventilate dead spaces by flow induction [3,4] (Figure 1).

This study using a VibrENT prototype (Figure 2) was undertaken to understand the effects of physical factors, pulsation, frequency, aerosol size, and nasal flow rate as well as sinus anatomy on sinus drug delivery efficiency and to obtain information how drug delivery and device features may be improved.

Materials and Methods

Nebulization efficiency was investigated using a novel human cast deposition model developed by PARI. 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).

0.5 mL of a Levofloxacin (LEV) solution (100 mg LEV/ml) was completely aerosolized into each nostril while the exit nostril was fit with a resistor and a filter for collection of expelled aerosol. Consequently, in total a label claim (LC) of 1 ml or 100 mg of LEV was administered in about 3 minutes.

A design of experiments (DoE) was used varying the sinus volume (SV) on 3 levels (7, 12 and 23 mL), the ostium diameter (OD) on 4 levels (1, 2, 3 and 6 mm) and droplet size at two levels (3.7 and 4.7 µm MMD). 12 randomized experiments, resulting in 72 sinus/ostium combinations, were carried out.

The effect of pulse frequency (0, 36 and 110 Hz) and flow rate (1.5, 3 and 7 l/min) was tested in 12 separate experiments with constant sinus volume (7 mL) and ostium diameter (6 mm) (Figure 8). Conversely, in total a label claim (LC) of 1 ml or 100 mg of LEV was administered in about 3 minutes.

Conclusion

It is possible to ventilate and deliver aerosol to the sinuses via pressure pulsations, but physical boundary conditions like droplet size, frequency and flow rate have to be considered.

Sinus diameter and volume strongly affect deposition efficiency but in contrast to current literature [5], sinuses deposition with narrow ostia (1 cm) is higher than with very wide ostia (6 mm), indicating that the VibrENT might be an option prior to surgery.

The PARI VibrENT delivers high amounts of drug to the nasal and paranasal cavities in-vitro.

Results

・ Total paranasal cavity deposition was highest (~20% of LC) with ostia of 1 and 3 mm in diameter and sinus volumes of 7, 12 and 23 ml when VibrENT was operated at flow rates below 3 l/min and a pulsation frequency of 36 Hz.
・ Delivery efficiency decreased at higher frequencies (Figure 6), higher flow rates and with larger aerosol droplets (Figure 7).
・ Omission of pulsation resulted in no drug deposition and a drop in nasal cavity deposition from more than 50% to about 6% (Figure 6).
・ Drug deposition to the sinuses is also significantly (p<0.01) affected by the ostium diameter and sinus volume, being lowest (~0.2% LC) at a large ostium diameter (6 mm) and a low sinus volume (7 mL) (Figure 8).

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Literature