Evaluation of the performance of sonic nebuliser to target maxillary sinuses

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1. Context

- Patients with cystic fibrosis (CF) suffer from **SINONASAL pathologies**: nasal obstruction, rhinosinusitis, sinonasal inflammation, PNS

(Fokkens et al., rhinology, EPOS2007, EPOS2012)

» **Severe & infected chronic rhinosinusitis**

- **MAXILLARY SINUSES (MS)** are recognized major infected sites *(with ethmoid and middle meatus)*

(Laube B, JAM, 2007)

In CF patients, **MS** are described as a **SOURCE (NICHE or RESERVOIR)** for *Pseudomonas aeruginosa* clones to proliferate & to diversify, for subsequent lung chronic infections.

(Hansen et al., ISME, 2012; Aanaes, 2011; Mainz JG et al., 2011 & 2009; Bendouah et al., ORL-HNS, 2006; Hoiby et al., 1989 to 2005)
2. Treatments

- Inhaled corticoïds (nasal sprays) +/- antibiotic per os (Grade A)

- Topical antibiotic NOT RECOMMENDED (Grade C)

  - However CF patients often need important antibiotic lavages (+/- sinus surgery) to reduce symptoms

NASAL SPRAYS

- Large particle size 20 to 200µm

- Drug deposition into nasal valve

- NOT for antibiotic

NASAL NEBULISERS

- Particle size 4µm

- Target infected sites

- Available for antibiotic delivery

- Specific device use VIBRATIONS to improve sinus deposition

Therapeutic OPTION for topical administration

(Suman et al., PharmRes 1999; Moeller et al., ORL HNS, 2010; Kundoor et al., PharmRes, 2009)
3. **Objective**

To study the deposition of antibiotic in nasal cavities, in particular in maxillary sinuses (therapeutic interest), obtained with this specific nasal nebuliser.

*IN VITRO* in a **plastinated head model**.

To evaluate this nasal nebuliser for intranasal administration.

*IN VIVO* in **healthy volunteers** (by scintigraphy method).
4. **Sonic nasal nebuliser**

- The Atomisor NL11SN®/AOHBOX® (DTF medical, France) produces a **sonic aerosol** by adding a **100 Hz SOUND**.

- **Both nostrils** administration via a **nasal plug**.

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**Breath-enhanced jet nebuliser**

**NASAL PLUG**

**AIR SOURCE**

**SONIC AEROSOL**

**Right MS ostium**

**Inferior turbinate**

**Right nasal fossa**

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**Sonic nasal nebuliser**

**Air source**

**Nasal plug**

**SONIC AEROSOL**
5. IN VITRO study

**METHODS**

- Plastinated head model (NASAL model) with free exterior access to MS

- GENTAMICINE nebulisations (10min) with the sonic NL11SN (with 100Hz sound) in comparison with a nebuliser without sound

  *To TEST the effect of the sound*

- Gentamicine is **collected** into MS (rinse) and **quantified** (FPIA test)
IN VITRO RESULTS

Gentamicine concentration collected into MS of head model, after CLASSIC or SONIC NL11SN nebulisations.

$0.68 \pm 0.27$

$<0.27$

$\times 3 \; p<0.05$

Duran et al., ANORL, 2012, In Press
7. IN VIVO Study

METHODS

- 7 non-smoking healthy male volunteers (21 to 36 years).

- STEP 1: NASAL Ventilation with $^{81m}$Kr gas
  with and without NL11SN to test the effect of the sound

- STEP 2: NL11SN nebulisations with $^{99m}$Tc-DTPA (10min)

- Gamma camera images: NASAL CAVITIES and THORAX

  ➔ % of aerosol deposited into NASAL & LUNGS were quantified.
8. IN VIVO study

IN VIVO RESULTS

- Krypton images of nasal cavities (Anterior view)
- Aerosol deposition into volunteers’ airways (& NASAL profile)

1-A (without sound)
Nasal cavities

1-B (with sound)
Penetration into maxillary sinuses

<table>
<thead>
<tr>
<th>AIRWAYS</th>
<th>Deposition (%)</th>
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<tbody>
<tr>
<td>UPPER AIRWAYS</td>
<td>73 ± 10%</td>
</tr>
<tr>
<td>LOWER AIRWAYS</td>
<td>27 ± 10%</td>
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(Le Guellec et al., RDD 2009; Vecellio et al., IJP, 2011)
9. Conclusions

**IN VIVO study** demonstrated

The **100 Hz SOUND** used by the **NL11SN nebuliser** improves MAXILLARY SINUSES VENTILATION;

The **sonic nasal NL11SN** optimizes **NASAL AEROSOL DEPOSITION**;

**Tested IN VITRO** with an antibiotic, the **100 Hz SOUND used by the NL11SN** increases the **DEPOSITION OF AEROSOL** into MAXILLARY SINUSES (INFECTED SITES);
10. **Sinus drug deposition?**

- **Q:** Is the aerosol drug deposited into MS efficient? i.e. is a local effect induced?
- **Proposition:** Comparison with an effective lung treatment

**Effective CF Lung Deposition**

**IN VITRO DRUG DEPOSITION**

- 45 mg
  - Lung tobramycin deposition
  - Total lung tissue surface $\cong 130 \text{ m}^2$
  - $= 0.036 \mu g/cm^2$

- 3.31 µg
  - Both MS gentamicin deposition
  - Mean MS volume 17 cm$^3$
  - Both MS tissue surface = $61.8 \text{ cm}^2$
  - $= 0.052 \mu g/cm^2$

**MS Drug Deposition Equivalent to Lung Deposition**

- Durand et al., 2012, in press
- Lenney et al., CF, 2011; Emirzeoglu et al., ANL, 2007
SINUS aminoside deposition, expressed per unit of tissue surface:
- is equivalent to a LUNG aminoside deposition recognized as effective lung treatment in CF patients.
- can be considered sufficient to induce a therapeutic local effect.

In definitive, the NL11SN seems to be adapted for CF patients to treat sinus infections.
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