SONIC NEBULISATION IN RHINOLOGY

Chronic rhinosinusitis (CRS), a common condition affecting hundreds of millions of people worldwide, is often treated with saline solution or corticosteroids. In this paper, Laurent Vecellio, Ing, Phd, Scientific Director, and Sandrine Le Guellec, Ing, Scientist, Biology & Medical Research, both of DTF's Aerodrug division, and Gilles Chantrel, Co-Chief Executive Officer, DTF Medical, describe a sonic nasal nebuliser that operates with an acoustic frequency of 100Hz, and clinical studies demonstrating its efficacy in the delivery of treatments for CRS.

INTRODUCTION

The human nose daily ensures air conditioning of inspired air, the first immune protection of the lower airway and olfactory functions.[1] For many years the nasal cavities have been considered as a route for drug administration, justified by positive attributes such as the rapid onset of clinical effects, no first-pass metabolism, non-invasiveness, the improvement of patient comfort and hence compliance.[2,3]

The development of intranasal therapeutics concerns three major fields of interest linked to pharmaceutical targeting: topical delivery, systemic delivery and, more recently, central nervous system delivery. Topical delivery allows high doses of medication to be administered in the target organ and minimises adverse effects.[4] The middle meatus, the maxillary sinuses and the ethmoid regions have been identified as important target sites for drug delivery to treat inflammation and infections in rhinology pathologies locally.[5] Vasoconstrictors, anti-histaminics and corticosteroids are delivered by nasal spray to treat nasal congestion (or obstruction) and nasal mucosa inflammation during acute or chronic rhinologic pathologies such as allergic rhinitis, rhinosinusitis and nasal polyposis.

However, the nasal sprays currently available on the market are limited by their formulations and technologies. The drug fraction delivered beyond the nasal valve is low,[6] and most deposited drug is rapidly removed by mucociliary clearance and eventually eliminated through the digestive tract. Furthermore, dose delivery to the target sites depends on many factors, such as nasal

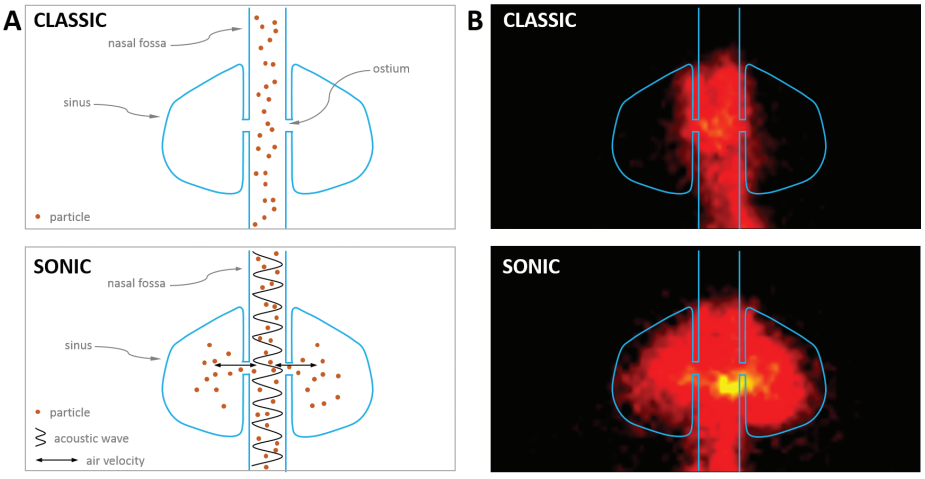

Figure 1: A. Sonic effect on ventilation and aerosol penetration in a sinus model acting as a Helmholtz resonator (SONIC versus CLASSIC). B. Influence of acoustic frequency waves on krypton gas penetration in human maxillary sinus (Scintigraphic imaging of front of nasal cavities of a healthy volunteer). (Adapted from Durand et al.[9])

Dr Laurent Vecellio
Scientific Director
Aerodrug
T: +33 2 47 36 60 61
E: laurent.vecellio@med.univ-tours.fr

Sandrine Le Guellec
Scientist, Biology & Medical Research
Aerodrug
T: +33 2 47 36 61 95
E: sandrine.leguellec@med.univ-tours.fr

AeroDrug
Aerosoltherapy R&D department of DTF medical
Faculté de médecine,
10 ter bd Tonnellé
37032 Tours
France

www.aerodrug.com

Gilles Chantrel
Co-CEO, DTF Medical
T: +33 4 77 74 51 11
E: gilles.chantrel@dtf.fr

DTF Medical
La Diffusion Technique Française
19 rue de la Presse,
42003 Saint Etienne
France

www.dtf.fr

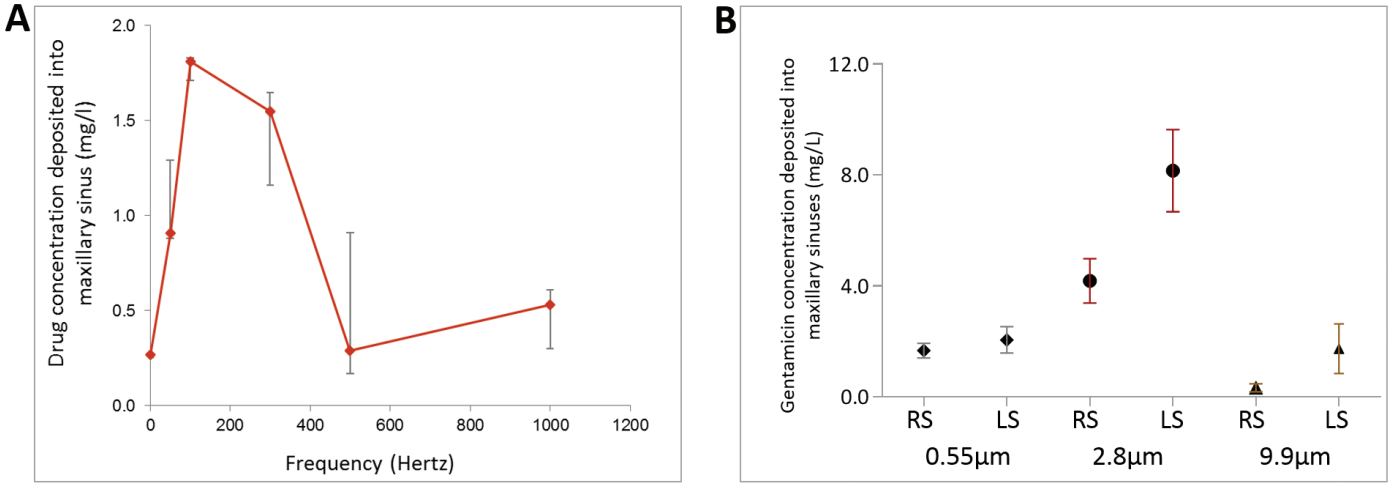

Figure 2: A. Effect of acoustic wave frequency on drug deposition in the maxillary sinuses of a nasal cast (mean±SD). (Adapted from Durand et al.[16]) B. Influence of the MMAD of the sonic aerosol on drug deposition in the right (RS) and left (LS) maxillary sinuses of a nasal cast (mean±SEM). (Adapted from Leclerc et al.[19])

plug penetration or orientation, resulting in considerable variability in terms of drug deposition and which may explain some failures in patient treatment.

Nebulisers produce finer particles than sprays (3 µm *versus* 30 µm) resulting in a more homogeneous drug deposition in the nasal cavities and improved targeting of the anatomic region of interest.[6,7] Adding an acoustic frequency enhances ventilation [8,9,10] and aerosol deposition [11,12] in the sinonasal cavities. Nebulisers are considered as medical devices, and drugs such as antibiotics, which are not available in nasal spray form, can be loaded in their reservoir.

There is no clear international recommendation for the use of nebulisers in rhinology,[4] but 45% of general practitioners and 78% of ENT specialists in France prescribe nebulisation for the treatment of upper respiratory tract diseases.[13,14]

SONIC NEBULISATION

The sinuses are air cavities connected to the nasal fossa by small openings (ostia). They are a source of local infection and thus a target zone for drug delivery. Due to their anatomy and poor ventilation, drug access is difficult.

In 1959, Guillerm and Badre [15] demonstrated that aerosols can be diffused in the sinuses by adding a sound. The theory is based on the principle of the Helmholtz resonator, whereby the sinus with its ostium resonates at a natural frequency when the air is excited (like air in a bottle). Outside air acts like a piston and increases the ventilation and penetration of aerosol into the sinus to target the local infection (Figure 1). Durand *et al* [16] demonstrated that 100Hz is the optimal frequency for delivering drugs to the maxillary sinuses in a nasal cast model (Figure 2). The Atomisor NL11SN®, a sonic nebuliser developed by DTF Medical, uses this 100Hz sound with a jet nebuliser generating the aerosol (Figure 3). It is a breath-enhanced nasal jet nebuliser improving drug administration during patient inspiration and reducing drug leakage in ambient air during exhalation. It uses a two-prong nasal plug in a soft material allowing an airtight seal with the nostrils, ensuring good aerosol delivery, minimising noise, the treatment of both nasal cavities simultaneously, and patient comfort.

Figure 3: Nasal nebulisation with the sonic nebuliser (Atomisor NL11SN®).

INFLUENCE OF PHYSICAL PARAMETERS ON DRUG DELIVERY

The deposition of sonic aerosol into nasal cavities has mainly been studied using artificial models of human nasal cavities (nasal cast). Artificial ventilation can be added to the nasal cast in order to simulate the nebulisation therapy conducted by a patient inhaling and exhaling through the nebuliser. Plastinated head model [11] and epoxy nasal replica based on CT-scan [17] are currently the nasal casts that best represent human anatomy and have recently been validated as being able to predict human nasal aerosol deposition.[18] The influence of different parameters in these nasal casts on the deposition of sonic aerosols has been evaluated with radioactivity and chemical tracers and drugs.

Sonic aerosol performance has been studied to assess whether it can enhance the penetration of the drug into the maxillary sinuses. Indeed, several studies have demonstrated that the addition of a 100Hz sound during aerosol administration significantly increases the penetration and deposition of aerosol in the maxillary sinuses whatever the sinus anatomy.[8,9,11,19,20] Durand *et al* showed penetration of a radioactive tracer in the maxillary sinuses of a plastinated head model [8] and a three-fold increase of deposited gentamicin.[9, 20]

The deposition of inhaled aerosols is also influenced by the particle size produced by the nebuliser. Studies have been conducted

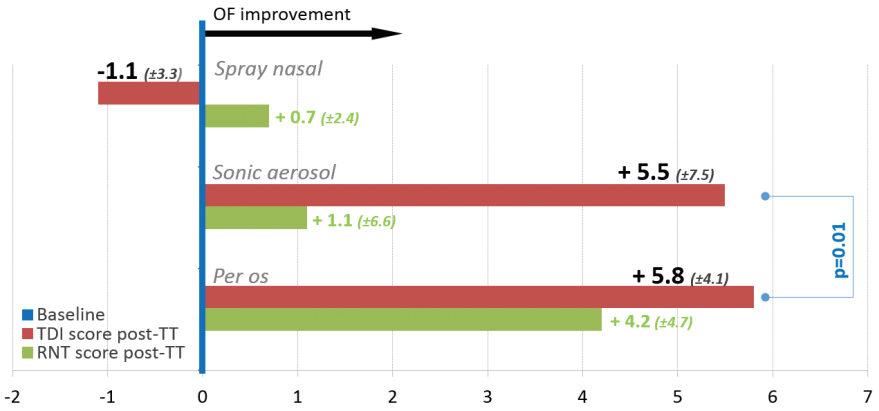

Figure 4: Score of olfactory functions (TDI and RNT scores) obtained from CRS patients before and after 16 days of corticotherapy with oral Medrol® (prednisolone), Pulmicort®, NL11SN® nasal sonic aerosol (budesonide), and Rhinocort® nasal spray (budesonide). (Adapted from Reychler et al.[22])

on nasal casts to determine the optimal particle size targeting different regions of interest.[17] A quantification of the fluorescein tracer deposited in each region was performed after nasal administration of aerosols with 2, 4.5, and 9.5 µm of mass median aerodynamic diameter (MMAD). With a constant inspiratory airflow rate (7 L/min), the aerosol mass deposited in the nasal cast increased with MMAD from 2.1% for the 2 µm aerosol to 43.5% for the 9.5 µm aerosol .

The increase in deposition was greater in the nose and nasal valve (+25% of deposition between 4.5 µm and 9 µm aerosols) than in the turbinate region (+8% of deposition between 4.5 µm and 9.5 µm aerosols). Deposition in the ethmoid was not affected by the increase in MMAD. A 2 µm MMAD aerosol can cross the nasal valve and produces more homogenous deposition in the nasal cavities.

The influence of particle size on aerosol deposition in the maxillary sinuses was investigated by Leclerc *et al*, who studied gentamicin deposition with an epoxy nasal replica and radioactive tracer deposition (SPECT-CTscan imaging) with a plastinated head model. They obtained optimal maxillary sinus deposition for the nebuliser generating a 2.8 µm aerosol with 100Hz sound, compared with results obtained with 9.9 µm, 0.55 µm, 0.23 µm aerosols with 100Hz sound. These studies demonstrate the interest of using a sonic nebuliser generating 2-2.8 µm of MMAD to target the anatomical regions of interest for treating rhinology pathologies (maxillary sinuses, ethmoid and turbinates).

Nasal deposition also depends on inspiratory airflow rates. A correlation between aerosol deposition and inspiratory flow rate was obtained in a study by Francis *et al* for a 4.5 µm MMAD aerosol (R^2>0.82 for nose added to nasal valve and, turbinates). The turbinate region was less affected by the increase in inspiratory airflow rate (+1% from 2-15 L/min) than the nose added to nasal valve (+5% from 2-15 L/min). An increase in maxillary sinus deposition was measured when the airflow rate increased (0.01% at 2 L/min to 0.09% at 15 L/min), but no correlation was obtained. Contrasting results were obtained by Leclerc *et al* with a nasal cast; using 0.55 µm and 2.8 µm aerosols with a 100Hz sound, they found that the amount of drug deposited in the maxillary sinuses increased when inspiratory flow rate decreased. The authors obtained 2-9 times more maxillary sinus deposition at 6 L/min than with standard inspiratory flow rate (sinus wave curve with a total of 15 L/min), demonstrating the influence of breathing patterns on drug deposition in anatomical regions of interest.

In conclusion, *in vitro* studies have demonstrated that an aerosol with an MMAD of 2-3 µm administered with the addition of a 100Hz sound, as performed by the NL11SN®, provides the optimal conditions for targeting the anatomical regions of interest for treating rhinology pathologies (maxillary sinuses, ethmoids and turbinates).

CLINICAL RESULTS

The positive impact of adding a 100Hz sound during radioactive gas (krypton) exchange between nasal fossa and maxillary sinuses has been demonstrated in healthy volunteers (see Figure 2B).[9,21] Vecellio *et al* found that 70% of the NL11SN® sonic aerosol was deposited in the nasal cavities of seven healthy volunteers, and 30% in the lungs; the pulmonary deposition resulted from the penetration of the small proportion of aerosol with a lower particle size. Study of radioactive deposition confirmed the homogeneous targeting of human nasal cavities, in particular the maxillary sinuses and ethmoid regions (respectively 0.5% and 1.1% of deposited aerosol).

Nasal corticotherapy has been evaluated recently for the treatment of olfactory disorders in chronic rhinosinusitis (CRS) patients with or without nasal polyps (respectively CRSwNP and CRSsNP). Reychler *et al* used the NL11SN® nebuliser to administer Pulmicort® (budesonide) in a sonic aerosol form and compared clinical results with those of Rhinocort® (budesonide) nasal spray and oral tablet Medrol® (prednisolone) therapy.[22] Treatment was conducted for 16 days, and the same dose of budesonide was administered to patients receiving nasal corticotherapy by spray or by sonic nebuliser. Clinical outcomes (Sniffin' sticks test, TDI scores) showed similar improvement of olfactory functions (OF) in patients receiving aerosol sonic treatment and oral treatment. No clinical benefit was observed for patients receiving the corticosteroid by nasal spray (Figure 4).

The clinical benefit for OF was the same for the two drugs administered at two different doses (32 mg of budesonide by sonic nebuliser *versus* 352 mg of oral methylprednisolone). This clinical response differed when the same drug was administered with the same dose via two different nasal devices (sonic nebuliser *versus* nasal spray).

The authors also found a significant difference in terms of nasal deposition of the budesonide depending on the nasal device used; the same dose of budesonide penetrated twice as far when administered by the NL11SN® than when it was administered by the nasal spray (*in vitro* study).

Reychler *et al* suggested that there is a relationship between the distribution of the deposited drug in the nasal cavities and the clinical effect observed in patients. A second study was performed on CRS patients with olfactory disorders. Goektas *et al* studied the OF (Sniffin' sticks test) of 15 CRS patients receiving oral prednisolone for 12 days (80 mg/day decreasing to 10 mg/day), and of 18 CRS patients receiving prednisolone by sonic aerosol for 12 days (total dose of 25 mg).[23] The authors also reported a significant OF improvement in all patients treated with oral prednisolone or by sonic aerosol ($p<0.05$). Both groups were equivalent for TDI scores after two months and after six months of follow-up.

Topical nasal administration with sonic nebulisers is also of clinical interest for antibiotic therapy. In particular, patients suffering from nasal polyposis (NP) often present recurring suppurations even after ethmoidal

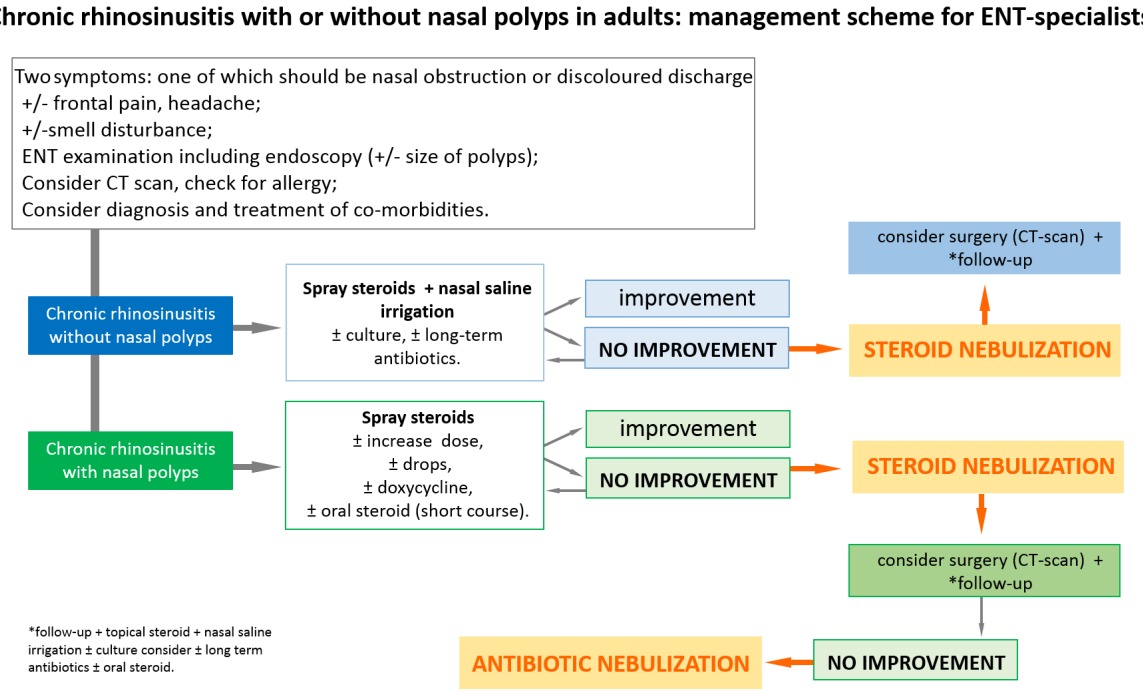

Figure 5: Proposal management scheme of chronic rhinosinusitis patients with and without nasal polyps for ENT specialist based on EPOS2012 scheme, including steroid and antibiotic sonic nebulisation. (Adapted from Fokkens et al.[4])

surgery. A preliminary study was conducted to determine the type of bacteria involved in these post-operative exacerbations (after radical ethmoidal surgery). Pathogenic bacteria isolated from 48 patients (80% of patients in the study) were predominantly identified as *Staphylococcus aureus* (60%) and Gram-negative bacteria. Nearly all the microorganisms were susceptible to antibiotics, including the aminoglycosides.[24] Based on this preliminary prospective study, tobramycin (150mg, Erempharma, Levallois-Perret, France) was selected for nasal nebulisation treatment in 72 post-operative NP patients (>2 months) who presented nasal suppurations (<3 months). After seven days of treatment, significant eradication of the bacteria was reported, compared with serum physiology treatment (respectively 46.9% and 17.4% of eradication; p=0.02).[25,26]

DISCUSSION

The prevalence of CRS in Europe is 10.9%, with marked geographical variation (range 6.9-27.1).[27] In the US, CRS affects 30 million people per year.

Corticosteroid sprays and nasal saline irrigations are recommended [4] for treating mild CRS, with additional oral antibiotics for moderate and severe cases. Surgery is considered when there is no improvement with these treatments. International recommendations do not include nebulisation to treat CRS.

Sonic nebulisation has been developed since 1981 and optimised to target anatomic regions to treat inflammation and infections in rhinology pathologies. The addition of a 100Hz sound and particles of 2-3 µm MMAD have been demonstrated to provide the optimal conditions for drug deposition in anatomical regions of interest including the maxillary sinuses. Sonic nasal nebulisation leads to deposition in the lung (70% in the nasal cavity and 30% in the lung), in the same way as nebulisers used in lung treatment produce deposition in the upper airways (30% in the upper airways and 70% in the lungs). This lung deposition could be a problem for future nasal drug development, with potential lung toxic effects. A new device named Easynose has been developed by DTF to allow fine particle administration via the nose without lung deposition and improving nasal and sinus deposition.[21]

Recent clinical studies [22,23,26] using the sonic nebuliser have demonstrated the efficacy of corticosteroids for olfactory functions and antibiotics for the eradication of nasal bacteria.

Comparison of sonic nebulisers and nasal sprays has shown that topical corticosteroid treatment is more effective with sonic nebulisation, demonstrating the possible interest of nebulisation when nasal spray treatment fails.

Comparison of sonic nebulisation and the oral route for corticosteroid administration has shown that similar clinical efficacy can be achieved by nebulisation with a lower dose, indicating that nebulisation could reduce side effects and be used to administer higher doses to improve clinical outcomes. These results support the interest of using sonic nebulisation for CRS patients, prior to (and after) sinus surgery.

Recently, a French consensus for nebulisation practices in rhinology [28,29] has been published, recommending the use of a sonic nasal nebuliser for the treatment of suppurative and oedematous rhinosinusitis, subacute rhinosinusitis (duration of symptoms 4-12 weeks), exacerbation of chronic rhinosinusitis and recurrent and suppurative post-operative rhinosinusitis (>1 month). This consensus, published by medical doctors, confirms the role of nasal nebulisation as a major tool for treating rhinology pathologies. Figure 5 proposes the inclusion of sonic nebulisation as a supplementary tool in the CRS-management scheme for ENT specialists.

Nasal nebulisation is of particular clinical interest for the treatment of rhinology pathologies and should be considered as an alternative and efficient drug administration route, in the same way as oral nebulisation is preferred under certain clinical conditions for lung treatment (compared with oral tablets, pMDI or DPI drug administration).

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