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SFORL Guidelines

Consensus document for prescription of nebulization in rhinology

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ABSTRACT

Objectives: The French Society of ORL set up a work group to draw up a consensus document on the prescription of nebulization in rhinology. The document deals with the principles of and indications for rhinologic aerosol therapy.
Materials and methods: The work group's methodology followed the rules published by the French health authority (Haute Autorité de santé [HAS]) in January 2006: "Methodological foundations for drawing up professional guidelines by formalized consensus" (available on the HAS website at http://www.has-sante.fr). The method used is the short version (without editorial group) of the RAND/UCLA Appropriateness Method; the short version was chosen because this particular consensus conference was dealing with a very precise topic with very few experts in the field.
Results: Sonic aerosol therapy with nasal plug is the preferred modality, delivering treatment into the middle meati. The group recommends that drugs with market authorization for use in bronchopulmonary pathology should be nebulized in two 10-minute sessions per day for at least seven days. Indications for rhinologic aerosol therapy are: purulent edematous rhinosinusitis, subacute rhinosinusitis (4–12 weeks' evolution), exacerbations of chronic rhinosinusitis, and postoperative (>1 month) rhinosinus suppuration. Audiometric monitoring is required in iterative aminoside nebulization.
Conclusion: Rhinologic aerosol therapy can be used in purulent edematous rhinosinusitis, subacute rhinosinusitis, exacerbations of chronic rhinosinusitis and postoperative rhinosinus suppuration. The rules for prescription contained in the present document optimize efficacy.

1. Introduction

Nebulization is a widely used means of drug delivery to the upper and lower airways. Its theoretic advantage over classic means of delivery is that it directly reaches the target organ, avoiding systemic side effects and enhancing local efficacy. It is mainly used in pneumology; pneumologic nebulization shows proven efficacy for drugs such as bronchodilators, corticosteroids, mucolytics and antibiotics. The number of specialties in which lower-airway nebulization has market authorization and the number of studies published on the subject testify to the liveliness of the field. Few publications, however, have been devoted to ENT nebulization, and only one drug (gomenol) has market authorization here. On the other hand, the NUAGES survey of the use and perspectives of nebulization in general and specialized medicine (*nébulisation, usages et avenir en médecine générale et spécialisée*), performed in France in 2005, clearly showed that prescription of nebulization is most widespread in pneumology with ENT coming a very close second, 89% of ENT physicians prescribing aerosol therapies by nebulization [1]. While there are no guidelines for ENT nebulization, the

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NUAGES survey revealed practitioners' interest in and actual use of it. The consensus document requested by the SFORL aims to draw up guidelines as an aid to prescription of ENT nebulization.

2. Theoretic foundations and aerosol deposition

Aerosols are defined in physical terms as a system of particle suspension in gas. In medical aerosols, particle size is of the order of a micrometer. The aerosols produced by different generation systems have particles of differing sizes. Two main parameters describe particle size distribution: mass median aerodynamic diameter (MMAD) represents median particle size; and geometric standard deviation represents the scatter around the MMAD. The main physical mechanisms determining particle deposition in the airway are directly governed by particle size [2]. In nasal inhalation, larger particles are mainly deposited in the upper airway: 90% for 10 μm particles, 50% for 5 μm and 10% for 2 μm [3,4]. On entering the nostrils, the aerosol is intercepted by the vibrissae, which constitute a first large particle filter. The nasal valve, where upper airway diameter is smallest and air-speed highest, is the site of maximal deposition [3]. The turbinate region is the second most important bottleneck inducing deposition, with diameter varying over the nasal cycle. Sinus deposition is controversial but seems to be due to pressure difference between the sinus and nose [5]; it varies with individual anatomy and is proportional to ostial diameter; the optimal particle size to reach the sinuses may be 0.7–10 μm [6].

In oral inhalation, the guidelines identify deposition sites according to particle size [7]. Particles with aerodynamic diameter >5 μm are deposited mainly in the oral cavity, larynx and trachea; those with aerodynamic diameter 4–5 μm, in the bronchi; and those with aerodynamic diameter 0.5–4 μm, in the deep lung. Particles <0.5 μm are too fine to be deposited and get exhaled.

Ventilation parameters also affect deposition. Particle speed is determined by the generator and influenced by the individual patient. Rapid inspiration accelerates the particles and increases deposition in the upper airway. Individual airway anatomy strongly affects inspiration hydraulics and thus deposition.

It follows that nasal nebulization is preferable for targeting the nasal cavities. A nasal plug should be used; in patients for whom this is not feasible, a mask is preferable to a mouth end-piece.

Guideline 1
Nebulization should enable deposition over the entire nasal cavity surface, including medial meatus – unlike sprays, with which deposition is essentially anterior. Strong agreement.

3. Aerosol generators

There are various ways of producing ENT aerosols. Two categories may be distinguished. Sprays are ready-to-use devices already containing the drug; nebulizers need to be prepared by introducing the drug into the reservoir. Sprays are portable, for instantaneous dose delivery; nebulizers tend to be heavier and require several minutes' inhalation.

Sprays produce large particles (10–150 μm) at high speed, with deposition mainly in the anterior centimeters of the cavity [8]; the entire dose is deposited within the cavity. Nebulizers produce slower and smaller particles (1–10 μm), with more distal deposition [9–11]; they can target regions (e.g., sinus) not reached by sprays, with significantly longer drug residence (1.2 h vs. 14 min) [10]. Even so, only 5-20% of the mass in the reservoir gets deposited in the nasal cavity; the shortfall is due to a large residual quantity of drug left in the nebulizer and a large amount of aerosol lost to the air during expiration.

There are three main types of nebulizers: pneumatic nebulizers use compressed air; ultrasonic nebulizers use high-frequency piezoelectric quartz vibration; and mesh nebulizers use the vibration of a microperforated mesh. Pneumatic nebulizers have the advantage that they can be used with any liquid preparation and are robust and easy to maintain. Ultrasonic nebulizers do not work with certain preparations: e.g., with high viscosity or in suspension. Mesh nebulizers are subject to viscosity and surface tension effects, but are silent in operation and small in size.

Some devices have additional functions to enhance upper airway deposition. The sonic function adds a sound-wave to the aerosol to improve maxillary sinus penetration and deposition. Studies on the operating principles of these devices go back to the 1950s: the principle is to induce acoustic hyperpressure in the ostium, displacing the air and aerosol toward the maxillary sinuses. Several in-vitro studies on models of varying sophistication demonstrated the benefit of introducing sound [12–14], but only very recently has it been demonstrated in humans, in scintigraphic studies [10,15,16]. Sinus deposition is 3–5-fold greater [17] than with a nebulizer without sonic boost.

The manosonic function is a derivative of this sonic function, adding hyperpressure to create positive pressure in the nasal cavities; this is automatically applied in the nose at the exact moment of swallowing, so as to transfer the aerosol toward the Eustachian tube. Systems with this extra function are known as manosonic aerosol generators.

Guideline 2
Nebulizers with additional sonic vibration are recommended in rhinosinus pathology. Ultrasonic aerosols are suitable for bronchopulmonary pathology. Strong agreement.

Guideline 3
Nasal plugs are to be preferred. Mouth end-pieces are reserved to laryngeal and bronchopulmonary applications. Strong agreement.

Guideline 4
Oro-nasal masks cause deposition on the face and within the oral cavity and should be reserved to patients unable to use a nasal plug. Strong agreement.

Guideline 5
Active substances should not be diluted for last-generation nebulizers, as residual volume is slight. Relative agreement.

Guideline 6
Nebulization time depends on drug volume, and should not exceed 10 minutes. Strong agreement.

Guideline 7
In the absence of studies of rhinosinus pathology, the work group recommends nebulization of drugs with market authorization in bronchopulmonary pathology: budesonide, beclomethasone, tobramycin, colimycin. Relative agreement.

Guideline 8
In the absence of clinical efficacy studies of drug associations in aerosol rhinosinus pathology, the work group advises against nebulizing associations in a given session. Disagreement.

Guideline 9
The work group advises against nebulizing oily preparations (risk of lipid pneumonia) or those containing sulfites (risk of bronchospasm) or other empiric preparations. Relative agreement.

Guideline 10
The work group recommends nasal cavity lavage ahead of nebulization. Relative agreement.

4. Clinical studies

Clinical studies of nasal nebulization are few, and with small cohorts. The first prospective study, in 2001, reported fosfomycin aerosol nebulization 3 times per week for four weeks in 28 chronic rhinosinusitis (CRS) patients; symptoms and endoscopic aspect improved in 60% of patients, and posterior rhinorrhea in 88% [18]. The second prospective study, in double-blind versus placebo, analyzed tobramycin nebulization in 20 CRS patients after failure of medical and surgical treatment; patients received nebulization of either physiological saline or 80 mg tobramycin three times per day for four weeks. Symptoms (obstruction, pain, nasal mucosa edema, posterior nasal discharge and secretion), quality of life and endoscopic parameters were assessed at end of treatment and at four weeks' follow-up. Symptoms and quality of life showed significant improvement ($P < 0.05$) in both arms; tobramycin nebulization was associated with faster resolution of pain at two weeks ($P < 0.05$), with no significant difference by 4 weeks. Tolerance was the same in both arms ($P < 0.05$) but tobramycin induced nasal cavity congestion [19].

In 2002, Vaughan and Carvalho assessed the microbiological impact of antibiotic nebulization versus standard oral or intravenous administration in 42 patients undergoing sinus surgery for CRS, comparing cultures from sinus endoscopy samples at end of treatment. Nasal obstruction and facial pain showed improvement with nebulization; nebulized antibiotic aerosol therapy resolved infection in 76% of cases [20]. Scheinberg and Otsuji, in the same year, reported a prospective study of antibiotic nebulization in 41 patients with exacerbated CRS resistant to surgical and medical (oral antibiotic) therapy. Treatment lasted 3-6 weeks; antibiotics comprised cefuroxim (285 mg twice daily), ciprofloxacin (70 mg twice daily) or tobramycin (90 mg twice daily). Symptoms (obstruction, pain, rhinorrhea and malaise) improved with treatment in 83% of cases [21].

In 2008, Videler et al. reported a double-blind prospective crossover study against placebo in 14 patients with exacerbated CRS resistant to surgical and medical treatment, testing the efficacy of bacitracin/colimycin nebulization associated to oral levofloxacin. All patients received 500 mg levofloxacin twice daily for 2 weeks ahead of nebulization and, after randomization, received 8 days' twice daily nebulization of either bacitracin/colimycin (6.64 mg/5.12 mg/8 mL) or physiological saline. Symptom severity was self-assessed on VAS and quality of life on the SF36 questionnaire; efficacy was assessed on nasal endoscopy. Facial pain was reduced in both groups at end of study ($P < 0.05$); symptomatology and quality of life were identical; endoscopy found no difference between the two groups [22].

Guideline 11
Nebulization is recommended in purulent edematous rhinosinusitis, subacute rhinosinusitis (4–12 weeks' evolution) and exacerbated chronic rhinosinusitis. Relative agreement.

Guideline 12
Nebulization is recommended in persistent postoperative rhinosinus suppuration (> 1 month). Strong agreement.

Guideline 13
Two nebulizations per day should be prescribed for at least seven days. Relative agreement.

Guideline 14
Audiometric monitoring is recommended in iterative rhinologic aminoside nebulization. Relative agreement.

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