Review

Nebulized Therapy. SEPAR Year

Casilda Olveira, Ana Muñoz, Adolfo Domenech

A UGC de Enfermedades Respiratorias, Hospital Regional Universitario de Málaga, Instituto de Biomedicina de Málaga (IBIMA), Facultad de Medicina, Universidad de Málaga, Málaga, Spain

A R T I C L E  I N F O

Article history:
Received 29 January 2014
Accepted 10 May 2014
Available online 31 October 2014

Keywords:
Nebulized therapy
Nebulizers
Nebulized antibiotics
Nebulized mucolytics
Bronchodilators

A B S T R A C T

Inhaled drugs are deposited directly in the respiratory tract. They therefore achieve higher concentrations with faster onset of action and fewer side effects than when used systemically. Nebulized drugs are mainly recommended for patients that require high doses of bronchodilators, when they need to inhale drugs that only exist in this form (antibiotics or dornase alfa) or when they are unable to use other inhalation devices. Technological development in recent years has led to new devices that optimize pulmonary deposits and reduce the time needed for treatment. In this review we focus solely on drugs currently used, or under investigation, for nebulization in adult patients, basically bronchodilators, inhaled steroids, antibiotics, antifungals, mucolytics and others such as anticoagulants, prostanoids, and lidocaine.

© 2014 SEPAR. Published by Elsevier España, S.L.U. All rights reserved.

T erapia nebulizada. Año SEPAR

R E S U M E N

Los fármacos inhalados se depositan directamente en el tracto respiratorio, con lo que se alcanzan altas concentraciones, con un inicio de acción más rápido y con menores efectos secundarios que si se emplea la vía sistémica. Los fármacos nebulizados se recomiendan fundamentalmente en pacientes que requieren dosis altas de broncodilatadores, cuando precisen inhalar fármacos que solo pueden administrarse nebulizados (como los antibióticos o la dornasa alfa) y si no son capaces de utilizar otros dispositivos de inhalación. El desarrollo tecnológico de los últimos años ha permitido contar con dispositivos que optimizan el depósito pulmonar y disminuyen el tiempo necesario para realizar el tratamiento. En esta revisión nos ceñiremos únicamente a aquellos fármacos que se administran –o están en investigación– en nebulización en pacientes adultos; fundamentalmente a los broncodilatadores, corticoides inhalados, antibióticos, antifúngicos, mucolíticos y otros como los prostanoides, los anticoagulantes o la lidocaína.

© 2014 SEPAR. Publicado por Elsevier España, S.L.U. Todos los derechos reservados.

Introduction

The inhaled route has been used for centuries to administer various substances and drugs. Inhaled drugs are deposited directly in the respiratory tract, and therefore achieve higher concentrations with faster onset of action and fewer side effects than when used systemically. The 3 modalities commonly used are pressurized metered-dose inhalers, dry powder inhalers, and nebulizers. As a general rule, nebulizers are not recommended if the drug can be administered using other devices. The European Respiratory Society recommends them for patients who require high doses of bronchodilators, when they need to inhale drugs that only exist in this form (antibiotics or dornase alfa), or when they are unable to use other inhalation devices.

Medicinal products for inhalation are developed with specific characteristics that are different to their systemically administered analogs. The efficacy of nebulization depends on many factors, including the characteristics of the medicinal product (size, shape, density, and surface tension of the particle), the anatomy of the airway, the patient’s inhalation technique, and the nebulization system. The size of the particles produced by a nebulizer depends on the properties of the solution and the
Table 1
Types of Nebulizers and their Characteristics, Advantages and Disadvantages.

<table>
<thead>
<tr>
<th>Types of nebulizers</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Examples of nebulizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultrasonic nebulizers</td>
<td>Nebulize large liquid volumes. Quieter than jet nebulizers</td>
<td>Very heterodisperse aerosol. Denature some drugs due to heat (antibiotics, DNase, corticosteroids). Do not nebulize suspensions. Cannot be used in children &lt;3 years 60%–70% of the volume is lost into the environment in the expiratory phase. Noisy, heavy compressors. High flow compressors (≥8 l/min) are recommended for nebulizing antibiotics, as they are faster and more effective than conventional ones (flow 6–8 l/min)</td>
<td>UltraAir®, NE-U17, Omron®</td>
</tr>
<tr>
<td>Pneumatic or jet nebulizers</td>
<td>Jet nebulizer with constant output</td>
<td>High flows. Can nebulize suspensions and solutions. Faster than ultrasonic nebulizers. Continuous aerosol flow in inspiration and expiration</td>
<td>High flow compressor: C600® or Turbeneb®, Turbey® Conventional compressor: Porta-neb®, PalmoAide®, Proneb® + Hudson Updraft II 1730® or DeVilbiss® (Marquest Whisper-Jet) or Pari LC Plus continuous® (Pari)</td>
</tr>
<tr>
<td></td>
<td>Jet nebulizer with Venturi effect active during inspiration</td>
<td>Provide high flows. Can nebulize suspensions and solutions. Faster than ultrasonic nebulizers. The inspired air is drawn out through the nebulizer area. Some have an expiratory valve</td>
<td>Compressor *</td>
</tr>
<tr>
<td>Dosimetric or modified release jet nebulizer</td>
<td>They release aerosol according to each patient’s inspiratory flow and only in the inspiratory flow or during part of it. Reduce the release of drug into the surrounding air to almost zero</td>
<td>Noisy, heavy compressors</td>
<td>Compressor * or Optine® pro® or Akita® jet favorite</td>
</tr>
<tr>
<td>Mesh nebulizers</td>
<td>Static mesh</td>
<td>Producible in homogeneous aerosol. Greater pulmonary deposition. They apply a pressure on the liquid so that it passes through the mesh generating the aerosol. Can operate with electricity or batteries. Small and quiet. Faster than jet nebulizers. Can nebulize suspensions and solutions</td>
<td>Less robust than jet nebulizers</td>
</tr>
<tr>
<td>Vibrating mesh (most commonly used)</td>
<td>The liquid passes through the holes in a vibrating mesh. Produce more homogeneous aerosol. Greater pulmonary deposition. Similar advantages to a static mesh. Some release the aerosol synchronized with the initial phase of inspiration. Can only be used for a specific medication. Reduce the release of drug into the surrounding air. Improve compliance</td>
<td></td>
<td>I-neb AAD®, eFlow® rapid with eBase® Controller. Aeroneb®Pro. Aeroneb®Go. Aerodose®. Allerca®</td>
</tr>
</tbody>
</table>

flow rate. The higher the flow rate, the smaller the size of the particles in the aerosol. Particles of between 1 and 5 μm are most likely to reach the correct sites in the branching tree and achieve the sought-after therapeutic effect.1–4 Nebulization devices or systems are composed of a nebulization chamber containing the liquid to be nebulized and from which the aerosol is generated, and an energy source to produce the mist. There are 3 types of nebulizers for clinical use: ultrasonic, jet (pneumatic) and mesh. Their main characteristics are summarized in Table 1. Nebulized drugs should preferably be administered using the nebulizers with which the clinical trials were conducted. Patients should be trained in their use, cleaning and maintenance. Technological development in recent years has led to new devices that optimize lung deposition and reduce the time needed to administer the treatment.1,4,5 In this review we will focus on currently available or investigational drugs for use in nebulization in adult patients.

Nebulized Bronchodilators and Corticosteroids

Various systematic reviews have shown that the 3 types of devices commonly used to administer inhaled bronchodilators and corticosteroids (pressurized inhalers, dry powder inhalers, and nebulizers) have a similar efficacy when used correctly.2–4,6,7 However, clinical practice has shown that some patients (particularly the elderly) with physical or mental limitations, or with serious disease, are unable to correctly use dry powder or pressurized metered-dose inhalers.8 These patients, together with those who prefer nebulizers to other inhalers, could benefit from nebulized drug delivery.2,3,9–13

Short-acting bronchodilators are those most often used in nebulization, with drugs such as salbutamol and ipratropium bromide being currently available. Their combined use has been found to obtain a 24% improvement in the FEV₁ compared to salbutamol alone, and a 37% improvement with respect to ipratropium.
bromide alone, in patients with chronic obstructive pulmonary disease (COPD).\textsuperscript{14} This treatment can improve quality of life even with concomitant use of another inhaler.\textsuperscript{15} Formoterol is the only long-acting bronchodilator available (as formoterol fumarate or arformoterol), although not in Spain. Various studies have demonstrated its effectiveness in the treatment of patients with COPD.\textsuperscript{16–18}

Nebulized corticosteroids,\textsuperscript{19–28} principally budesonide\textsuperscript{20–23} (although also flunisolide,\textsuperscript{24} fluticasone,\textsuperscript{25} and beclometasone,\textsuperscript{26,27}) , can be considered an effective alternative in patients with asthma or COPD who are unwilling or unable to use other inhalation devices (Table 2). In a study of elderly patients with asthma or COPD who found it difficult to use other devices, Marcus et al.\textsuperscript{28} observed less use of systemic corticosteroids and fewer visits to the emergency department when long-term treatment was maintained with nebulized corticosteroids. Maltais et al.\textsuperscript{21} compared the efficacy of nebulized budesonide and systemic corticosteroids in patients with COPD exacerbations and found no differences in FEV\textsubscript{1} improvement, hospital stay, or adverse effects. The use of higher or more frequent doses could be a safe alternative to systemic corticosteroids, without their accompanying side effects.\textsuperscript{23}

**Nebulized Antibiotics**

Nebulized antibiotics (NAB) (penicillin and streptomycin) were first used for the treatment of bronchial infection in the 1950s.\textsuperscript{29,30} These early attempts gave way to the use of a wider range of NABs, prepared from their intravenous formulation, essentially in cystic fibrosis (CF) patients with chronic *Pseudomonas aeruginosa* (PA) infection. They have also been used for the treatment of bronchial infection in non-CF bronchiectasis (NCFB), COPD, and in ventilator-associated pneumonia (VAP). All this has driven the commercialization of specific antibiotic preparations for nebulization (Table 3) and the launch of clinical trials with different antibiotics for inhalation (some in dry powder form, which will not be discussed here) in different diseases.\textsuperscript{29–33} NABs should preferably be administered using the nebulizers with which the trials were conducted.\textsuperscript{1–4,13,34}

**Nebulized Antibiotics in Cystic Fibrosis**

The benefit of prompt treatment with NABs (tobramycin [TIS]\textsuperscript{35–38,40–42} colistin\textsuperscript{19,40,43} or aztreonam-lysine [AZLI]\textsuperscript{44}) has been demonstrated in CF patients with early PA infection, as they achieve high rates of eradication and delay the onset of chronic bronchial infection.

Long-term administration of NABs has been shown to be effective in the treatment of chronic bronchial infection with PA in patients with CF:\textsuperscript{31,35–39,45–59} There are several options,\textsuperscript{35–38} including intermittent inhaled antibiotic therapy with 28 day treatment periods and 28 rest days using TIS\textsuperscript{31,45–49} or AZLI,\textsuperscript{38,55–59} or continuous treatment with colistin.\textsuperscript{36,39,50–52} Studies have already been conducted on other NABs not yet marketed in Spain, which have been shown to be effective and well-tolerated in patients with CF, such as levofloxacin,\textsuperscript{60,61} liposomal amikacin (Arikace\textsuperscript{62}),\textsuperscript{32,62} and the combination fosfomycin–tobramycin.\textsuperscript{93} Table 4 summarizes the main studies with NABs in patients with CF and chronic PA infection.

Exceptionally, other NABs are used in CF (prepared from their intravenous formulation) such as vancomycin for bronchial infection with methicillin-resistant *Staphylococcus aureus* (MRSA),\textsuperscript{63} or amikacin for treatment of rapidly growing atypical mycobacteria such as *Mycobacterium abscessus*\textsuperscript{64} or *Mycobacterium avium complex*\textsuperscript{65} as coadjuvant therapy and in combination with systemic antibiotics.

**Nebulized Antibiotics in Non-cystic Fibrosis Bronchiectasis**

There is less evidence in NCFB, but studies conducted with different NABs have observed an improvement in quality of life and symptoms, with a reduction in sputum volume and purulence and exacerbations, a decrease in bronchial and systemic inflammation, and lower density of PA colonies and colonies of other microorganisms, with variable eradication rates.\textsuperscript{29,33,67–84} Table 5 summarizes the main studies with NABs in patients with NCFB.

Two guidelines have so far been published, both of which essentially agree on the indications for NAB treatment in patients with NCFB. SEPAR guidelines\textsuperscript{33} recommend them in early colonization by PA (if eradication has not been achieved with oral ciprofloxacin), in chronic bronchial PA infection, and in chronic bronchial infection by other microorganisms when long-term oral antibiotic treatment is ineffective or there are adverse effects or resistances. British Thoracic Society guidelines\textsuperscript{67} recommend them in chronic PA infection when the patient has had more than 2 exacerbations in the previous year, or if they have significant morbidity.

**Nebulized Antibiotics in Patients With Chronic Obstructive Pulmonary Disease**

Patients with COPD can present persistent chronic bronchial infection, and a high prevalence of associated bronchiectasis has also been observed in those with moderate–severe disease, resulting in greater morbidity and poorer prognosis.\textsuperscript{85–88
According to Spanish COPD guidelines (GesEPOC), patients with the COPD frequent exacerbator phenotype with associated bronchiectasis and chronic bronchial infection are candidates for long-term or cyclical antibiotic treatment, and SEPAR Guidelines on bronchiectasis can be applied to them for the control of chronic bronchial infection. Several clinical trials have recently been set up to evaluate the safety, tolerance, and pharmacokinetics of formulations for inhaled use of levofloxacin and ciprofloxacin in patients with COPD, as well as their effectiveness in preventing exacerbations. Dal Negro et al. in an uncontrolled study, investigated the effect of nebulized tobramycin (300 mg/14 days) on the inflammatory markers in bronchial secretions in 13 patients with severe COPD colonized by multi-resistant PA, and obtained a significant reduction in markers of inflammation and, during the 6-month follow-up period, in bacteriological density and severe exacerbations. The study by Steinfort and Steinfort with nebulized colistin also included 4 patients with severe COPD chronically infected with multi-resistant Gram-negative bacteria; they observed an improvement in quality of life and a reduction in lung function decline.

### Nebulized Antibiotics in Ventilator-associated Pneumonia

Some studies have shown positive clinical results with NABs as adjuvant therapy for ventilator-associated pneumonia (VAP), with improved clinical severity scores, less microbial resistance and use of systemic antibiotics and/or fewer days of intubation. Studies range from the prevention of VAP to adjuvant therapy for the intravenous treatment of pneumonia caused by Gram-negative bacteria and the treatment of pneumonia caused by PA or multi-resistant Acinetobacter. Inhaled colistin has been shown to be effective as adjuvant therapy for the VAP fundamentally caused by multi-resistant pathogens (Acinetobacter and PA), with good bacteriological and clinical response.

Palmer et al., in a randomized, double blind placebo-controlled trial, included intubated patients who received NAB treatment according to Gram-stain (gentamicin 30 mg every 8 h for Gram-negative and vancomycin 120 mg every 8 h for Gram-positive) or placebo. NAB improved the clinical signs of pneumonia, reduced episodes of VAP, bacterial resistance, and the use of systemic antibiotics, and also facilitated weaning. In another randomized, placebo-controlled study, vancomycin in aerosol succeeded in eradicating the microorganism in 4 out of 5 patients with MRSA as the VAP causative agent. Although these cohorts were small and the results must be confirmed with larger trials, they suggest that aerosol therapy may be useful against MRSA.

The addition of antibiotics in aerosol form to systemic antibiotics may be considered in patients with multi-resistant microorganisms, in those who do not respond to systemic antibiotics, or in VAP.

### Pneumonia Caused by Pneumocystis jiroveci

Pentamidine in aerosol form is a relatively well-tolerated alternative to oral agents in the primary and secondary prevention of pneumonia caused by *P. jiroveci* in patients with HIV or other immunosuppressive states, such as hematopoietic stem cell transplant recipients.

### Antifungals

*Aspergillus fumigatus* infection is the most common infection in lung transplant recipients. Inhaled amphotericin is the most common preventive strategy. It has good distribution at pulmonary level without modifying surfactant lipid levels, and has very low systemic absorption. It comes in 3 presentations: amphotericin B deoxycholate, amphotericin B lipid complex, and liposomal amphotericin B. The latter 2 are the most widely used as they are well tolerated and have better pulmonary distribution.

Inhaled amphotericin for the prevention of invasive pulmonary aspergillosis has been used with good results in patients with hematological diseases with expected chemotherapy-induced neutropenia. It may also be an alternative to itraconazole or voriconazole treatment in patients with CF and allergic bronchopulmonary aspergillosis (ABPA). Proesmans et al. treated 7 patients with CF, ABPA, and difficulty in tapering steroids with amphotericin B deoxycholate or amphotericin B lipid complex.
demonstrating its efficacy and safety, with improved lung function and only 1 treatment failure.108

The pharmacokinetic results of an aqueous suspension of itraconazole for patients with ABPA have recently been published, reporting high and long-lasting lung tissue concentrations, which enable once daily administration with minimal systemic exposure.109

### Nebulized Mucolytics

Nebulized N-acetylcysteine has not been shown to be effective in COPD,10,9,11 CF12,13,30,37,111 bronchiectasis,3,67,58 or conclusively in idiopathic pulmonary fibrosis.112 A recent randomized study by Homma et al.113 found that nebulized N-acetylcysteine monotherapy could be useful in patients with early stage idiopathic

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Design</th>
<th>Treatment and duration</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramsey et al.11 (1999)</td>
<td>520</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>TIS twice daily for 38-day on-off cycles vs placebo</td>
<td>↑ FEV1, ↓ sputum volume, ↓ days hospitalization, ↓ use of i.v. and oral antibiotic treatment, ↑ QoL, TEN, and voice alteration</td>
</tr>
<tr>
<td>Murphy et al.47 (2004)</td>
<td>181</td>
<td>Randomized, open label, placebo-controlled</td>
<td>TIS twice daily for seven 28-day on-off cycles</td>
<td>Slows FEV1, decline, ↓ days hospitalization, ↓ use of other antibiotics. Dysphonia</td>
</tr>
<tr>
<td>Lenoir et al.48 (2007)</td>
<td>59</td>
<td>Randomized, open label, placebo-controlled</td>
<td>TIS twice daily in on-off period</td>
<td>↑ FEV1, ↑ weight, ↓ no. admissions, ↓ bacterial load. No ototoxicity or nephrotoxicity</td>
</tr>
<tr>
<td>Chuchalin et al.46 (2007)</td>
<td>247</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>TIS 300 mg twice daily for three 28-day on-off cycles</td>
<td>↑ FEV1, ↓ no. admissions, ↑ weight, ↓ bacterial load</td>
</tr>
<tr>
<td>Jensen et al.50 (1987)</td>
<td>40</td>
<td>Randomized, double-blind</td>
<td>Colistin 1 million U, twice daily for 90 days vs placebo</td>
<td>Less FVC decline, improvement in clinical parameters</td>
</tr>
<tr>
<td>Day et al.51 (1988)</td>
<td>14</td>
<td>Double-blind, cross-over</td>
<td>Colistin 1 million U, twice daily for 6 months vs placebo</td>
<td>↑ FVC, more coughing and sputum in patients with placebo</td>
</tr>
<tr>
<td>Hodson et al.52 (2002)</td>
<td>164</td>
<td>Randomized</td>
<td>Colistin 80 mg twice daily for 28 days vs TIS/4 weeks</td>
<td>Decrease in PA count in both groups. Improvement in pulmonary function with TIS</td>
</tr>
<tr>
<td>Retsch-Bogart et al.53 (2009)</td>
<td>211</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>AZLI 75 mg twice daily for 28 days vs placebo</td>
<td>↑ QoL (CFQ-R RSS), ↑ FEV1, ↓ hospitalization and hospital stay, ↑ weight, ↓ no. of PA colonies, ↓ cough</td>
</tr>
<tr>
<td>McCoy et al.54 (2008)</td>
<td>157</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>AZLI 75 mg twice daily for 3 months daily for 28 days vs placebo</td>
<td>↑ exacerbation-free period, ↑ QoL (CFQ-R RSS), ↑ FEV1, ↓ no. of PA colonies</td>
</tr>
<tr>
<td>Oermann et al.55 (2010)</td>
<td>268</td>
<td>Randomized, open-label</td>
<td>AZLI 75 mg twice daily for 28 days vs placebo</td>
<td>↑ QoL, ↑ FEV1, ↑ weight</td>
</tr>
<tr>
<td>Wainwright et al.56 (2011)</td>
<td>340</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>AZLI 75 mg twice daily in three 28-day on-off cycles vs TIS 300 mg twice daily in three 28-day on-off cycles</td>
<td>Improvement in FEV1, ↑ QoL (CFQ-R RSS), ↑ use of i.v. and oral antibiotic treatment, ↑ exacerbation-free period and ↑ weight in favor of AZLI</td>
</tr>
<tr>
<td>Assael et al.57 (2003)</td>
<td>151</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>AZLI 75 mg twice daily for 28 days vs placebo</td>
<td>↓ sputum density on day 28, ↑ FEV1, ↓ use antibiotic treatment, well tolerated</td>
</tr>
<tr>
<td>Elborn et al.58 (2013)</td>
<td>330</td>
<td>Open-label, randomized</td>
<td>Levofloxacin 240 mg twice daily vs TIS in three 28-day on-off cycles</td>
<td>Slows FEV1, decline, ↓ QoL, ↓ no. exacerbations, well tolerated, dysgeusia (metallic taste)</td>
</tr>
<tr>
<td>Trappell et al.59 (2011)</td>
<td>119</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Azithromycin 28-day on-off cycles vs TIS 300 mg twice daily in three 28-day on-off cycles</td>
<td>Slows FEV1, decline, ↓ sputum density</td>
</tr>
<tr>
<td>Clancy et al.60 (2013)</td>
<td>105</td>
<td>Randomized, double-blind, placebo-controlled</td>
<td>Liposomal amikacin once daily (70, 140, 280 and 560 mg) vs placebo for 28 days</td>
<td>Slows FEV1, decline ↑ QoL, ↓ sputum density on day 28. Well tolerated</td>
</tr>
</tbody>
</table>

AZLI, aztrexam lysine; CFQ-R RSS, Cystic Fibrosis Questionnaire-Revised; QoL, quality of life; FEV1, forced expiratory volume in the first second; FVC, forced vital capacity; PA, Pseudomonas aeruginosa; TIS, tobramycin solution for inhalation.
pulmonary fibrosis, because although there was no improvement in lung function, it did appear to halt deterioration.

Inhalation of dornase alfa (DNase) has been shown to be clearly effective in CF, but in bronchiectasis due to other etiologies it may be ineffective or even harmful, and therefore is not recommended (Table 6).

Inhalation of hypertonic saline solution (HSS) in patients with CF is effective, as it reduces exacerbations, improves quality of life, and slightly improves lung function.

In patients with NCFB, HSS may reduce sputum viscosity and exacerbations, and improve quality of life and lung function.

Nicolson et al. compared saline 6% with saline 0.9%, and found that both reduced colonization by microorganisms and exacerbations, while improving quality of life and lung function, with no significant differences between concentrations. HSS may also have immunomodulatory effects, and it has been observed that it may reduce interleukin-8 concentrations in sputum and bronchoalveolar lavage.

Clinical trials are currently ongoing in COPD with HSS and BIO-11006 inhalation solution, which could have anti-inflammatory effects and inhibit mucous secretion.

Other Nebulized Therapies (Table 2)

Alpha-1 antitrypsin (AAT). The role of nebulized AAT as an anti-inflammatory treatment in CF is currently being investigated. In a
randomized, double-blind study of 39 patients treated for 4 weeks with inhaled human recombinant AAT, the drug was well tolerated, but had a limited effect on inflammatory markers. In contrast, Griese et al. observed a decrease in the total PA load and in inflammatory markers in induced sputum with the inhalation of AAT. Nebulized l-arginine has recently been used in patients with CF and was found to be safe and well-tolerated, increasing nitric acid production with no evidence of changes in bronchial inflammation.

Magnesium sulfate. Various studies have assessed the role of magnesium sulfate in asthma exacerbation. A recent Cochrane review did not find significant improvements when magnesium sulfate was added to beta-agonist treatment. In a subsequent meta-analysis, magnesium sulfate was added to usual treatment with corticosteroids and beta-2 agonists; in adults, this nebulized treatment was associated with a significant effect on pulmonary function and a reduction in hospital admissions. Goodacre et al. compared the effect of intravenous magnesium sulfate versus nebulized magnesium sulfate and placebo in 1084 adults, and found no benefit in adding it to standard treatment, either in dyspnea or in the rate of hospitalizations. There is currently no evidence that nebulized magnesium sulfate in adult patients has any effect on asthma exacerbation.

 лидокайн. Лидокаин является местным анестетиком и антиаритмическим агентом. Введение лидокаяна в дыхательный рукав сокращает число приступов, вызываемых стимуляцией верхних дыхательных путей.

Iloprost. Iloprost is a prostanoid used to treat pulmonary hypertension. It is a synthetic analogue of prostacyclin. Iloprost is used in the treatment of pulmonary hypertension, particularly in patients with primary pulmonary hypertension, as a symptom-management treatment and for a reduction in the use of corticosteroids for symptom control. Although it has been shown to improve symptoms in some patients, its use is limited due to potential side effects such as flushing, headache, and nausea.

Furosemide. Furosemide is a loop diuretic used to relieve dyspnea via nebulized administration. It has been effective in patients with advanced cancer and severe dyspnea who do not respond to opiates. Various studies have shown that furosemide can reduce dyspnea, pH, blood pressure, and heart rate in patients with advanced respiratory distress syndrome (ARDS) and PAH, reporting improvement in gas exchange without any detriment to respiratory or hemodynamic parameters.

Iloprost was approved by the FDA in 2009 for patients with PAH and functional class III. Its effectiveness was initially demonstrated in patients who remained symptomatic despite treatment with bosentan and sildenafil, and has also been used as an alternative to intravenous or subcutaneous prostanooids.

Prostanoids. In pulmonary arterial hypertension (PAH), there are two drugs within the prostanoid group that can be inhaled: iloprost and treprostinil. Iloprost is an analog of prostacyclin authorized in Spain as inhaled treatment in adults with PAH and functional class III. Although there was an initial improvement in functional grade, in the long-term only a few patients remained stable with iloprost in monotherapy. There are studies that support its efficacy in combination with bosentan and sildenafil, and also as an alternative to intravenous or subcutaneous prostanoids.

Recent studies have explored the usefulness of iloprost in patients with acute respiratory distress syndrome (ARDS) and PAH, reporting improvement in gas exchange without any detriment to respiratory or hemodynamic parameters.

Inhaled treprostinil was approved by the FDA in 2009 for patients with PAH and functional class III. Its effectiveness was initially demonstrated in patients who remained symptomatic despite treatment with bosentan and sildenafil, and it has also been used as an alternative to intravenous or subcutaneous prostanoids.

Tuberculosis. Some attempts have been made to treat multidrug-resistant tuberculosis via the inhaled route, such as with dry powder capreomycin, or formulations of various tuberculostatics such as liposomal capreomycin. These formulations have shown good levels via aerosol delivery in experimental models. However, some characteristics of tuberculosis lesions, such as the existence of poorly aerated areas or growth of microorganisms in biofilms, reduce the efficacy of inhaled therapy.

Anticoagulants. Impaired alveolar fibrin turnover is a fundamental aspect of severe pneumonia. Clinical studies suggest that
natural coagulation inhibitors exert lung-protective effects via anticoagulant and possibly anti-inflammatory pathways. In experimental animals, the aerosolized administration of activated protein C, plasma anti-thrombin and hirudin significantly reduced pulmonary coagulopathy, with no changes in systemic coagulation. Plasma anti-thrombin treatment inhibits the spread of S. pneumoniae and histopathological damage in the lung. It has not been possible to confirm this effect in pneumonia caused by PA. In a systematic review of preclinical and clinical trials on nebulized anticoagulants, only 3 clinical trials on nebulized heparin were identified. These found an improvement in survival in patients with acute lung injury associated with smoke inhalation, and also a reduction in the number of days on mechanical ventilation.

Surfactant. One meta-analysis that analyzed the administration of exogenous surfactant in ARDS found that it might improve oxygenation but not mortality. However, a wide variety of routes of administration were used in this meta-analysis, which concluded that the bronchoscopic route may be most promising, as the rate of pulmonary deposition using the nebulized route only reaches 4%–5%.

Conclusion

Nebulized drugs are an effective therapeutic alternative in multiple respiratory diseases. Effective, rapid administration nebulization devices are currently available. The future will doubtless bring innovative drugs and new evidence that will allow us to resolve the many uncertainties that still exist.

Conflict of Interest

Casilda Oliveira has participated in expert committees and training activities promoted and funded by Chiesi, Gilead, Novartis and Praxis.

Adolfo Domenech has participated in training activities promoted and funded by Astra, Boehringer, Esteve, Glaxo, Novartis and Menarini.

Ana Muñoz has participated in training activities promoted and funded by Astra.

References


