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Original article

Inhalation therapy in cystic fibrosis

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Abstract. In Cystic Fibrosis (CF) inhalation of drugs to treat lung disease has been proven to be highly effective. An increasing number of drugs and devices have been developed for CF lung disease. In this article we will review the current status of inhaled medication in CF, including the various drugs, their modes of administration and indications, and their effects. We will address antibiotics, mucolytics/mucous mobilizers, anti-inflammatory drugs, bronchodilators and combinations of solutions. We will review the current knowledge on devices for inhalation therapy with regard to optimal particle sizes and characteristics of wet nebulisers, dry powder and metered dose inhalers. (www.actabiomedica.it)

Key words: cystic fibrosis; inhaled medication; inhalation devices

Introduction

Lung disease in CF is characterized by insufficient periciliary fluid, impaired clearance of airway secretions, an overactive inflammatory response, and chronic respiratory infections. As in many other chronic respiratory diseases, inhalation of therapeutic agents is an appealing way to treat lung disease topically, trying to maximize the dose at the site of disease while minimizing exposure to the rest of the body. Until recently, the number of medications available for CF treatment were limited and could easily be delivered by the aerosol devices available, including pressurized metered-dose inhalers (pMDIs), dry-powder inhalers (DPIs), and pneumatic jet or ultrasonic nebulizers. But with the explosion of CF-related research into disease mechanisms and potential treatments of the pathophysiologic cascade, those devices are no longer as appealing. Fortunately, we have coincidentally seen several advances in aerosol delivery technology that can be paired with new drugs to optimize inhaled drug delivery for CF patients (1).

The main benefit of pulmonary drug administration is the delivery directly to the location of the disease, while minimizing systemic exposure and toxicity. Pulmonary delivery is characterized by a rapid clinical response and the ability to bypass therapeutic barriers such as poor gastrointestinal absorption and first-pass metabolism in the liver (2). It can achieve a similar or superior therapeutic effect at a fraction of the systemic dose. For example, an oral dose of 2–4 mg salbutamol is therapeutically equivalent to 100-200 μg by inhalation. This is particularly important when considering aminoglycoside antibiotics for the treatment of Pseudomonas aeruginosa infections of the lung. Only low sputum aminoglycoside concentrations are achieved by the administration of relatively high intravenous doses, which carry the potential for systemic toxicity, whereas high sputum concentrations can be achieved by inhalation without the risk of systemic toxicity (3). Inhaled medications have been available for many years for the treatment of lung diseases like asthma and chronic obstructive pulmonary disease (COPD). Devices and formulations were designed for the administration of relatively low doses ranging from 6 to 500 μg (4). In recent years, the treatment for other diseases like CF and lung infections, as well as systemic diseases by pulmonary administration, has become more attractive. However, these therapies in general require higher doses to be effectively administered to the lung.

Materials and Methods

We used MEDLINE to search for studies that investigated the relationship between CF patients, inhaled medications and inhalation devices. The search included the following key words: Cystic Fibrosis; Inhaled medication; Inhalation devices.

Outcomes

Devices for pulmonary drug delivery

Systems for pulmonary delivery include pressurized metered dose inhalers (pMDI), soft mist inhalers, nebulizers and dry powder inhalers (DPI). Pulmonary delivery of high drug doses was carried out by nebulization of liquid formulations. The administration is time-consuming and regular cleaning and disinfection of the systems are required. This is particularly apparent for CF patients, where the time burden is immense when applying several aerosol therapies. DPIs have the capacity to deliver higher payloads of drug to the lung. In order to be effectively delivered to the alveolar region, particles must have an aerodynamic size between 1 and 5 μm (7). There has been continuous development of DPIs in order to improve the effectiveness of therapy.

Recently the Podhaler (T-326 Inhaler), which evolved from the Turbospin device, was approved to address the needs of high-payload delivery of engineered tobramycin and colistimethate sodium powder particles of around 50 mg. It was designed to have a low airflow resistance to allow patients to generate high airflow rates. Similar to the Turbospin device, the vortical airflow causes the capsule to spin while powder is shaken out of the two pierced holes and aerosolized.

Medications for Aerosol Delivery

A mucolytic medication degrades the polymeric structure of airway secretions. Usually this will reduce viscosity, and this in turn can decrease secretion adherence to the epithelium. A decreased viscosity can improve mucociliary clearance, although it may decrease the cough clearance of secretions (8). The archetype of the classic mucolytics is N-acetyl-L cysteine or NAC. Although NAC has been administered for decades as a mucolytic, it has never been shown to improve pulmonary function or clinical outcome in patients with CF, or other airway diseases. There is a secondary polymer network in sputum that is derived from the breakdown of inflammatory cells and bacteria. This secondary network is composed of highly polymerized DNA, which co-polymerizes with filamentous F-actin (9). This rigid co-polymer increases sputum tenacity and decreases the ability of to expectorate . Aerosolization of dornase alfa (Pulmozyme) has been used for more than 15 years for treating CF. Taken once daily, this medication improves pulmonary function and decreases the risk of pulmonary exacerbation (10). Medications have been developed that draw water into the airway (so called "hydrators"), including 7% hyperosmolar saline (11) and DPI mannitol (12). These also induce mucin secretion, and promote effective cough. There are other mucoactive agents, including mucolytics and mucokinetic agents that are in the early phases of testing for treating CF.

Aerosol antibiotics have been used for decades to treat chronic lung infection in bronchiectasis and CF. There are compelling data that demonstrate that aerosolized aminoglycosides like tobramycin and aerosolized colistimethate are effective in reducing the bacterial load in CF airways, improving pulmonary function, and decreasing the frequency of pulmonary exacerbation (13,14). Aztreonam lysinate for inhalation, using the Pari eFlow vibrating-mesh nebulizer, was approved by the FDA for the therapy of CF lung disease in early 2010 (15). Other aerosol antibiotics include tobramycin inhalation powder, colistimethate sodium powder and, under study, ciprofloxacin inhalation powder, levofloxacin, amikacine and others. One of the benefits of aerosolized antibiotics is that high concentrations of drug can be achieved in the proximal airway, far exceeding the MIC90 (minimum inhibitory concentration required to inhibit the growth of 90% of the organisms) of the antibiotic. This fosters the development of antimicrobial resistance. Patients with chronic bronchitis also have persistent lung infection and those with frequent exacerbations and infection with Pseudomonas are at high risk of developing bronchiectasis. It is possible that chronic bronchitis

exacerbations might be better treated by the combined use of aerosol and systemic antibiotics (16,17).

Discussion

Inhaled medications are primarily used by CF patients, mainly at home, for long periods of time. In these patients, practical issues, such as the time needed for drug delivery and the size of the device, are of interest. Cost is also an important parameter since newer devices appear to cost more than the previous ones. However, equally important parameters such as cost are compliant with treatment and quality of life. The less time these, mainly young, patients spend using a nebulizer along with the ability to carry their drug delivery system easily makes their life as close to normal as possible. This may counterbalance the increased cost paid for their treatment. We recognize the importance of quality of life, but the cost of the delivery system must not be an obstacle to the treatment of patients, especially if clinical effectiveness does not differ.

Conclusion

Clinicians should be aware of variability in performance of different nebulizer systems when used with different medications. The authors suggest that clinicians should look carefully at the available dosing data for the medication they wish to prescribe through the nebulizer system that they will be providing.

Technologies such as AAD and VMT have advantages over conventional systems in terms of treatment time, patient preference and adherence and can have advantages in deposition. As nebulized therapy has been shown to contribute greatly to daily treatment times and to burden of treatment, these technologies should be considered for use whenever possible (18).

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