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Dry powder inhalation versus wet nebulisation delivery of antibiotics in cystic fibrosis patients

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Inhalation of antipseudomonal antibiotics is a cornerstone in treating cystic fibrosis patients. It has shown to be effective in slowing down the process of pulmonary deterioration and decreasing the incidence of infectious exacerbations. The focus is now on innovating drug delivery devices, sometimes combined with specific drug formulations, which allow for the administration of large doses in a short time frame and in a reproducible way. Adaptive aerosol delivery devices are promising, but do not have a distinct position as yet because of the lack of long-term data. The position of dry powder inhalation of antibiotics in cystic fibrosis treatment is still confined to pilot studies. Until more clinical data are available, the suboptimal, conventional jet nebulisers are the mainstay in antipseudomonal inhalation therapy in cystic fibrosis.

Keywords: antibiotics, cystic fibrosis, dry powder inhalation, pulmonary drug delivery, wet nebulisation

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1. Introduction

Cystic fibrosis is a hereditary disease, caused by a mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Chronic infection and inflammation, predominantly caused by *Pseudomonas aeruginosa*, lead to progressive lung tissue destruction and a consequent loss of lung function and physical capacity. Preventing, limiting and treating this chronic infection and inflammation is the main objective in cystic fibrosis therapy, with the goal of improving survival and quality of life.

In the last four decades, scrupulous and centralised care of cystic fibrosis patients in the Western world has resulted in improved survival rates. In the US, the median life expectancy of infants born with cystic fibrosis has improved dramatically from 14 years in 1969, to 35 years in 2004 [1]. The introduction of antipseudomonal antibiotics for inhalation has been a major contributor to this improved survival [2]. Long-term inhalation treatment with antipseudomonal antibiotics has shown to be effective in slowing down the process of pulmonary deterioration, reducing the number of hospital admissions and improving nutritional status [3]. The next challenge is to further improve inhalation therapy with antibiotics in cystic fibrosis, in order to optimise inhalation efficiency and patient adherence.

2. Inhaled antibiotics in cystic fibrosis

Pulmonary administration of antibiotics in cystic fibrosis facilitates high concentrations of the drug at the target site in the lung, while decreasing systemic

exposure, thus reducing the risk of the introduction of antibiotic resistance and adverse effects.

Inhalation of antibiotics was initiated in the 1980s and subsequently studied. As a result, tobramycin and colistin sulphomethate are currently registered for inhalation treatment in cystic fibrosis patients chronically infected with *Pseudomonas aeruginosa*. Both tobramycin and colistin sulphomethate are either used for alternating months or, in most cases, for months or years at a time.

Cystic fibrosis is a disease of the peripheral airways [4]. To reach this part of the obstructed lung, an aerodynamic particle size of 1 – 5 µm (fine particle fraction) is mandatory. Combined with an appropriate inhalation flow, this particle size range has an optimal deposition potential in the lower airways. Particles > 5 µm will not reach the periphery of the lung, predominantly because of inertial impaction in the oropharynx, and large fractions of particles < 1 µm will be exhaled [4]. An inspiratory flow that is either too high or too low will intensify these effects. Therefore, to obtain optimal deposition probability in cystic fibrosis, the inhalation device should be able to deliver drug particles in the size range of 1 – 5 µm, at an intermediate inhalation flow.

2.1 Wet nebulisation

Nebulisation of antipseudomonal drugs started over two decades ago, by using commercially available drug products intended for intravenous use. From the 1980s and onwards, the main nebulising devices were based on ultrasonic or (conventional) jet flow techniques. Although ultrasonic devices have the advantage of a relatively short nebulisation time, the performance of these devices is significantly affected by physico-chemical properties of nebuliser fluids [5]; moreover, they are not universally applicable (e.g., dornase α) and are therefore limited in their therapeutic use.

Conventional jet nebulisers may be applied in order to administer a wide range of drug solutions over a wide dose and volume range. The choice of a nebuliser and compressor in combination with a drug solution for a specific pulmonary disease has become a more important issue over the years, as knowledge on inhalation characteristics has markedly improved. The performance of nebulisers differs in drug output, drug output rate, droplet size distribution and drug deposition in the target area of the lung [5], all in relation to the drug used. Lung deposition and clinical response are affected by the nebuliser and compressor used. A few studies have been performed on the combination of an antimicrobial drug for inhalation and a nebuliser-compressor combination. In contrast, a wide range of nebuliser compressor combinations are in daily use for inhalation of tobramycin and colistin sulphomethate.

Drug manufacturers are encouraged to market a drug for inhalation in combination with a specific inhalation device [6]. Tobramycin for inhalation (TOBI®; Novartis) is the only example of a drug registration that includes a recommendation for the use of a particular nebuliser [3].

Although this is a step forward, significant intersubject variability in pulmonary deposition between patients will remain, possibly affecting clinical response. Furthermore, nebulisation of a drug is an inefficient procedure, as ≥ 90% of the drug is lost [7]. An expiratory filter should be used to capture the exhaled antibiotic aerosol that will otherwise be lost to the environment, especially in areas where the antibiotic load is high (cystic fibrosis centres).

A subdivision into three common types of jet nebulisers can be made: constant output (unvented), breath-enhanced (vented) and breath-activated (including adaptive aerosol delivery [AAD] devices). The second type is presently state-of-the-art in cystic fibrosis inhalation therapy, and the third category may represent an interesting new option in pulmonary administration of drugs in cystic fibrosis patients.

AAD devices, also referred to as 'breath-actuated nebulisers', are wet nebulisers designed to deliver an inhaled drug in a predictable and constant manner to the periphery of the lung. The first AAD nebuliser (HaloLite®; Profile Respiratory Systems) became available in 1997. More recently, the I-neb® AAD® (Respironics) was introduced. Due to a high efficiency and the mesh technology used, the I-neb may provide a comparable (peripheral) lung dose compared to a conventional nebuliser drug dose with a smaller drug volume in a shorter time frame [8,9]. The eFlow *rapid*® (PARI) electronic nebuliser is another example of a device based on mesh technology. Whether these devices will contribute significantly to the treatment of cystic fibrosis patients is a subject for future studies. So far, studies on AAD nebulisers in cystic fibrosis have not shown a difference in clinical outcome between AAD devices and conventional nebulisers [8,10]. Also, no data are available on the performance after long-term every day use. In terms of cystic fibrosis treatment, this category of nebulisers is promising, but because of the lack of long term data, they do not have a distinct position as yet.

2.2 Dry powder inhalation

Dry powder inhalation in cystic fibrosis is still in its infancy. Only a few studies on this subject have been published, and all studied dry powder inhalation systems that were in an early stage of development. Tobramycin (80 mg in 6 actuations) was studied in 14 healthy volunteers and compared with liquid nebulisation; the dry powder inhalation system was found to be more efficient [11]. A gentamicin dry powder dose (180 mg in 6 actuations) using a Rotahaler® (GSK) was studied in 40 non-cystic-fibrosis patients undergoing routine bronchoscopy [12]. In another study, gentamicin dry powder (160 mg in 32 actuations), administered using a Clickhaler® (Innovata Biomed), was studied in 3 cystic fibrosis-patients and 7 non-cystic fibrosis patients with bronchiectasis [13]. Both administrations were compared with liquid administration of gentamicin. The studies showed pulmonary deposition of the drug, but no

conclusive proof for equivalence between wet and dry inhalation could be demonstrated. Dry powder inhalation of colistin (colistin sulphate 25 mg [14] and colistin sulphomethate 25 mg [15]) in two actuations has been studied in healthy volunteers and cystic fibrosis patients, and compared with conventional jet nebulisation of 158 mg (2 million units) of colistin sulphomethate. No equivalence between the colistin sulphomethate dosages was demonstrated, but lung deposition efficiency was improved by a factor of 2.7 using the Twincer® (University of Groningen) dry powder inhaler [15].

In summary, the position of dry powder inhalation of antibiotics in cystic fibrosis treatment is still confined to pilot studies. Future perspectives are promising, but long-term studies are needed to assess the value of dry powder antibiotic inhalers in cystic fibrosis.

3. Future perspectives

As yet, no ideal inhalation device for the administration of antibiotics to cystic fibrosis patients is available, but attempts to develop such a device are being made. However, in terms of the diversity in technical developments and drug formulation requirements, it is mandatory to keep the total costs of inhalation treatment within a realistic range and to perform pharmacoeconomic research, as state-of-the-art treatment should be within reach for every patient with cystic fibrosis. This is a shared responsibility of scientists, drug manufacturers, manufacturers of inhalation devices, national and international regulatory authorities and prescribers.

Significant improvements in the development of dry powder inhalers for cystic fibrosis treatment are to be expected, as many potential improvements have not yet been explored.

The present developments, such as the Twincer inhaler, are promising [15-17]. In addition to its simple design, the concept of a single use disposable inhaler is an advantage in preventing antibiotic resistance.

However, large long-term studies are required to assess the value of all newly developed devices in combination with a drug for the cystic fibrosis population.

As well as colistin and tobramycin, other antipseudomonal antibiotics for inhalation, such as ciprofloxacin [101], are also under investigation.

4. Conclusion

The inhalation of antipseudomonal antibiotics has become a cornerstone in treating cystic fibrosis patients. As this approach has proven to be successful, extensive attention is now given to the technical aspects of inhalation. The focus is on innovating drug delivery devices, sometimes combined with specific drug formulations, which allow for the administration of large doses in a short time frame and in a reproducible way. The ultimate aim is to prevent, limit and treat lung damage in order to maintain and improve quality of life. Unfortunately, there is insufficient data on the clinical benefits for cystic fibrosis patients to be able to justify the use of new inhalation devices filled with antipseudomonal drugs. Until more information is available, the suboptimal conventional jet nebulisers are the mainstay in anti-pseudomonal inhalation therapy in cystic fibrosis.

5. Expert opinion

The majority of cystic fibrosis patients are confronted with extensive and time-consuming drug administration, several times a day. Although inhaled antibiotics have significantly contributed to the improved life expectancy of cystic fibrosis patients, administration of nebulised antibiotics has a major impact on their daily life. Every option to improve this life-long routine should be investigated. Rapid administration of an inhalation dose with a small device, which is easy to use, able to perform efficiently, reproducible and reliable, reflects the ideal situation. Furthermore, the patient should be protected from the development of, and the exposure to, resistant bacteria. This makes a disposable inhaler system preferable.

Next to technical innovations, the development of effective antibiotics to combat *Pseudomonas aeruginosa*, *Burkholderia cepacia* and other Gram-negative bacteria will remain an ongoing quest. It is likely that these approaches will result in further improvement in clinical progress and life expectancy of cystic fibrosis patients.

The cystic fibrosis population is estimated at ~ 100,000 patients worldwide, with a high likelihood of underreporting and underdiagnosing, especially in developing countries [102]. In terms of cost-effective drug development for manufacturers, this population is small, making this field unprofitable for innovative pharmaceutical companies. Therefore, an opportunity has been created to develop drugs in the framework of an orphan drug programme in Europe and the US. So far, this has only been a theoretical gain, as it has not resulted in a new, commercially available, antipseudomonal drug and/or drug application device for inhalation for cystic fibrosis patients. Therefore, it is important that pharmaceutical companies, scientists and clinicians persevere in their (joint) efforts to improve life expectancy and quality of life.

The use of inhaled tobramycin and colistin sulphomethate in cystic fibrosis is complicated by the lack of knowledge on the optimal intrapulmonary dosage of these drugs, and the inter-device and inter-individual variability between patients, resulting in a highly variable pulmonary drug deposition.

Every professional who is involved in the treatment of cystic fibrosis patients with inhaled drugs should be aware of the fact that wet nebulisation, with a conventional jet-nebuliser of a fixed drug dose, results in poor lung deposition, as only ~ 10% (5 – 12%) of the drug reaches the

small airways [7,11]. Therefore, drug loss in conventional wet nebulisation is greater than after dry powder inhalation or breath-actuated wet nebulisers. Theoretically, AAD devices perform better in terms of drug loss, but due to the lack of clinical studies in cystic fibrosis patients, it is difficult to evaulate these nebulisers. This is also valid for dry powder inhalers, as future studies will have to determine their added value in treating cystic fibrosis patients.

From a theoretical point of view, dry powder inhalation seems to have the best properties for cystic fibrosis patients ≥ 8 years of age, as dry powder inhalation can be performed rapidly with a small device, which, depending on the technique used, does not need electricity to operate. Moreover, a dry powder inhaler may be designed as a disposable device for single use, preventing cross contamination and exposure of cystic fibrosis patients to resistant bacteria.

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