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Review article

Developments and strategies for inhaled antibiotic drugs in tuberculosis therapy: A critical evaluation

M. Hoppentocht *, P. Hagedoorn, H.W. Frijlink, A.H. de Boer

Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, The Netherlands

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ABSTRACT

Inhaled antibiotics have been a valuable tool in treating pulmonary infections in cystic fibrosis patients for decades, and the pulmonary route is now becoming increasingly interesting for other infectious diseases like tuberculosis too. Especially with multidrug and extensively drug-resistant tuberculosis emerging, great effort is put into the improvement of pulmonary antibiotic administration to fight this global threat. Several reviews have been written on inhalable antibiotics, giving clear overviews of the compounds of interest. Furthermore, various formulation studies and administration strategies are on-going with these compounds. What is often missing is a critical evaluation of these developments. Several risks may be involved varying from obtaining insufficient local drug concentrations to adverse side effects and unwanted changes in physiological processes from the excipients used. In this manuscript, the pros and cons and feasibility of recent advances in pulmonary antibiotic tuberculosis therapy are presented and critically evaluated. Furthermore, the advantages of dry powder inhalation over wet nebulisation for inhaled antibiotics in developing countries where prevalence of tuberculosis is highest are discussed. It has to be concluded that a greater effort in good inhaler development and more research in the physicochemical properties of the compounds of interest are needed.

1. Introduction

There is a growing interest in the pulmonary route for the administration of antibiotic drugs. Inhaled antimicrobial therapy is particularly interesting for diseases like cystic fibrosis (CF), tuberculosis (TB), non-CF bronchiectasis (non-CFB) and pneumonia [1–4]. The advantages of this route of administration are well recognised and quite pronounced [1–3,5]. Compared to orally or parenterally given drugs, inhaled drug doses delivered directly to the target area may be considerably lower to achieve the same local effect. This results in a strong reduction in adverse systemic side effects compared to oral or parenteral administration. On the other hand, with the same dose administered directly to the respiratory tract, much higher local drug concentrations can be obtained. This may eradicate strains of micro-organisms that are considered resistant against the same drug in the same dose given via the systemic circulation as resistance is often related to the drug concentration.

CF is the disease for which most experience exists with inhaled antibiotics to date [1,6]. Pulmonary administration of antibiotics in CF has the potential to preserve lung function and to reduce the frequency of hospital admission [7–9]. CF therapy is mostly a lifetime lasting therapy and most of the recent developments in drug delivery to CF patients aim to increase the efficacy of administration, minimise the risks of bacterial resistance building and prevent patient re-infection [10]. In contrast, the administration of inhaled antibiotics against TB and other infectious diseases is currently still in its infancy and much can be learned for TB from the experience of the CF community [11]. Also unlike CF, TB is an infectious disease and particularly because of the rapidly growing multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains considered as a world-wide threat because of high risk of transmission. It may therefore, not be surprising that there are a much greater interest and a higher effort put in finding new ways to control this disease compared to CF. This is reflected by the great number of studies on *Mycobacterium tuberculosis* (*Mtb*), including those in which specific new strategies are explored [3,12].

Several reviews have recently been written on inhalable antibiotics giving clear overviews of the compounds of interest and the various formulation studies and administration strategies performed with these compounds [2,12–14]. What is often missing is a critical evaluation of these developments. Some of the formulations presented require complex preparation techniques and/or involve the addition and inhalation of excipients, occasionally in large quantities, of which the long-term toxicity is still uncertain. Some strategies may seem to be based on sound reasoning and

* Corresponding author. Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands. Tel.: +31 50 363 3254; fax: +31 503632500.
E-mail address: m.hoppentocht@rug.nl (M. Hoppentocht).

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hopeful expectations, but their efficacy still has to be proven. In many ways physiological and immunological mechanisms may be affected to yet unknown extent on the long-term. Also, local drug concentrations may be insufficient and promote bacterial resistance building rather than to guarantee effective eradication and finally, the technical feasibility of some of the strategies presented is still highly uncertain. Therefore, approaches may be highly interesting from an academic point of view, but eventually these developments have to contribute to a better therapy. The aim of this manuscript is not to review the antibiotics and their formulations presented in the literature for inhalation, but rather to evaluate the technical feasibility, therapeutic efficacy and safety of the different approaches and strategies undertaken for inhaled antibiotics in TB therapy. We did not attempt to list all the examples for the different formulation types, but we selected representative papers for a critical evaluation.

2. Inhalable antibiotics

Many existing and new drugs may in future be considered suitable for direct delivery to the lungs and they have extensively been reviewed before [13,14]. They include first-line anti-TB drugs like rifampicin, pyrazinamide and isoniazid, and second-line anti-TB drugs from the groups of aminoglycosides (e.g. gentamycin, kanamycin, and amikacin) and fluoroquinolones (e.g. moxifloxacin and gatifloxacin). Particularly isoniazid, rifampicin and pyrazinamide seem interesting for pulmonary application against MDR and XDR TB, as it is expected that much higher local concentrations with these drugs can be achieved via this route of administration [15]. This might make resistant *Mtb* strains in the lungs susceptible to these drugs again. Second-line antibiotics in TB treatment like the aminoglycosides gentamicin and kanamycin have already been used as adjunctive salvage inhalation therapy in patients with persistent smear-positive pulmonary TB [11]. Amikacin (with the widest antimicrobial spectrum of all aminoglycosides [16]), capreomycin (effective against species that have become resistant to other agents [17]) and moxifloxacin (a fourth-generation fluoroquinolone with very good activity against *Mtb* [18,19]) are to be considered for pulmonary application in TB therapies too. Other nowadays orally and parenterally given drugs considered suitable for pulmonary administration in TB therapy are examples like clofazimine and linezolid. Finally, some new compounds like TMC207, PA-824, OPC-67683, PNU-100480, AZD-5847, SQ109 and BTZ043 are in development for application against TB and could be interesting for pulmonary application as well [13,14]. A greater variety of antibiotics being available for inhalation is urgently needed to compensate for an increasing bacterial resistance of *Mtb* against a growing number of currently used anti-TB drugs.

3. Antibiotic drug formulations

With a few exceptions, most of the early studies with inhaled antibiotics are known from the period 1965 to 1995 [20,21] for drugs like tobramycin, colistimethate sodium, carbenicillin, gentamycin and ciprofloxacin [22,23], but it lasted till 1998 before the first formulation (tobramycin: TOBI®, Novartis) against *Pseudomonas aeruginosa* (*Psa*; in CF therapy) received approval from the US Food and Drug Administration (FDA) [20]. Most of these examples are for nebulised antibiotics, and studies with dry powder formulations are relatively scarce. Because of the many disadvantages of classic nebulisation techniques [24,25] there is a strong desire to further improve the therapies with inhaled antibiotics with new formulations and matching devices. For diseases like TB there are several arguments in favour of dry powder formulations. Such formulations can be stable and administered with cheap, disposable devices which makes them suitable for developing countries in warm climates in which (MDR and XDR) TB prevalence is highest. For a few drugs (e.g. rifampicin and clofazimine) dry powder formulations seem the only alternative considering their low water solubility. Ideally, inhaled drugs as dry powders should be crystalline for maximal stability. Spray dried, spray–freeze dried and freeze dried powders from solution are mostly fully amorphous which increases their moisture sensitivity. Water uptake by amorphous powders reduces their glass transition temperature and this may result in re-crystallisation and solid bridge formation between the particles which deteriorates dispersion. Other (physico-chemical) drug properties that can play a role in the dispersion efficiency and inhaler retention are the cohesiveness, flowability and compactability, which depend on the chemical nature of the compound as well as on the size and shape distribution and surface properties of the drug particles.

Most developments on anti-TB drugs for dry powder inhalation so far are primarily feasibility studies which have not yet resulted in clinical studies or commercialisation. Many of these studies have been reviewed by Traini and Young [2]. They often focus on specific delivery strategies by making use of liposomal drug formulations for sustained drug release or drug containing insoluble microspheres for targeting of the alveolar macrophages. They also often disregard the relevance of an appropriate inhaler to be used for the administration. Antibiotic dry powder inhalation has a number of specific problems and challenges, most of them relating to adequate dispersion and inhalation of the large powder quantities. Early studies with drugs like gentamicin and colistin have shown that high powder doses can well be tolerated by the patients, although this may depend on the chemical structure of the antibiotic or the specific salt used [26,27]. Dividing of the dose over a number of successive inhalations may nevertheless be necessary for different reasons. Smaller inhaled powder quantities could increase patient acceptance by reducing cough reactions and chest tightness. In addition, they may improve the performance of the inhaler. As an example, a single TOBI® dose from the capsule based Podhaler® consists of four capsules filled with approximately 45 mg of powder each (of which 28 mg is the active drug). A large number of inhalations are likely to increase inhalation errors and worsen patient adherence to the therapy because of the increased total administration time however. For these reasons, the number of inhalations per dose should be kept as low as possible. Some formulations presented in the literature contain high excipient contents which increases the total amount of powder to be inhaled even further. Such formulations with low antibiotic payloads (<50%) for replacement of oral or parenteral administration seem to have no practical value for TB therapies. They are unlikely to make it to the market, particularly when they additionally require complex multi-step manufacturing processes which make them expensive [28–38]. Minimising the use of excipients makes the performance of the dry powder inhaler (DPI) strongly dependent on the physico-chemical properties of the drug itself. Dispersion and retention depend on the chemical nature of a compound as well as on its particle size and shape distribution, water content, anomeric composition, etc. But the precise effect of all solid state properties is not known and the same powder may disperse well in a ventüri-like disperser, whereas dispersion in a whirl, circulation or impaction chamber may be insufficient and/or lead to extreme retention. The opposite result may be obtained for another class of antibiotics, which is the reason why more knowledge of the relevance of the solid state properties to dispersion and retention is needed. As a response to that, the inhaler design can be adjusted to the requirements for good dispersion and low retention of a particular class of antibiotics. Even for a fairly well documented drug like tobramycin, the information in the public domain is confined to polymorphism and related