Aerosol Delivery of Antimicrobial Agents During Mechanical Ventilation: Current Practice and Perspectives

Argyris Michalopoulos\textsuperscript{1,2}, Eugenios I. Metaxas\textsuperscript{2} and Matthew E. Falagas\textsuperscript{2,3,*}

\textsuperscript{1}Director, Intensive Care Unit, “Henry Dunant” Hospital, Athens, Greece; \textsuperscript{2}Alfa Institute of Biomedical Sciences, Greece; \textsuperscript{3}Department of Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA

Abstract: Critically ill patients, who develop ventilator-associated pneumonia during prolonged mechanical ventilation, often require antimicrobial agents administered through the endotracheal or the tracheotomy tube. The delivery of antibiotics via the respiratory tract has been established over the past years as an alternative route in order to deliver high concentrations of antimicrobial agents directly to the lungs and avoid systemic toxicity. Since the only formal indications for inhaled/aerosolized antimicrobial agents is for patients suffering from cystic fibrosis, consequently the majority of research and published studies concerns this group of patients. Newer devices and new antibiotic formulations are currently off-label used in ambulatory cystic fibrosis patients whereas similar data for the mechanically ventilated patients do not yet exist.

Keywords: Antibiotics, delivery system, inhalation, nebulization, ventilation.

INTRODUCTION

Critically ill patients, who develop ventilator-associated tracheobronchitis or pneumonia during prolonged mechanical ventilation, often require antimicrobial agents administered through the endotracheal or the tracheotomy tube. The delivery of inhaled/aerosolized antibiotics, to these patients, has some advantages when compared to systematic administration. The greater concentrations of the antimicrobial agents achieved in the respiratory tract and the lesser systematic adverse events are some examples \cite{1}. Main adverse event is acute bronchoconstriction, especially when the intravenous preparation of antimicrobial agent has been used for aerosol administration. These preparations contain antioxidants and preservatives that may contribute to bronchospasm \cite{2}. Formulations, specially prepared for aerosol delivery, have been found to be less irritating than the parenteral formulations.

Several investigators have shown that the aerosol delivery was efficient in mechanically-ventilated patients. A number of antibiotic agents, including aminoglycosides, beta-lactams and polymyxins, have been administered as aerosols in critically ill patients, with no history of cystic fibrosis (CF) \cite{3}. Aerosol delivery of antimicrobial agents during mechanical ventilation is associated with the following advantages: The antimicrobial agent is delivered directly to the respiratory tract with less frequent and mild systemic adverse effects since a small fraction of the inhaled antibiotic is absorbed minimizing systemic bioavailability; Higher lung concentrations of the antimicrobial agent can be obtained with smaller aerosol doses; The onset of antimicrobial effect is faster.

However, the efficacy of aerosolized delivery has not been evaluated in any randomized, controlled trial and their use in aerosolized form in non-CF patients, has not been approved neither by the Food and Drug Administration (FDA) nor by the European Medicines Agency (EMEA) \cite{4-6}. In addition, all clinical studies evaluating the efficacy of inhaled antimicrobial agents usually have small sample size, lack of appropriate controls, and inadequate blinding of participants \cite{7}.

PULMONARY ANTIBIOTIC DELIVERY TO THE INTUBATED PATIENT: CURRENT PRACTICE AND CONCERNS

A variety of devices that deliver drugs directly to the lung can be employed during mechanical ventilation. Since most of the data relating to pulmonary delivery of antibiotics have been obtained from spontaneously breathing patients \cite{8} data from \textit{in vitro} assays are very useful in guiding aerosol therapy during mechanical ventilation. In the past years \textit{in vitro} and \textit{in vivo} studies have contributed to a better understanding of the factors that influence inhaled drug delivery in mechanically-ventilated patients, such as the ventilator circuit and the artificial airway. Factors influencing inhaled drug delivery in mechanically ventilated patients include the ventilator mode and settings, heat and humidification of inspired gas, density of the inhaled gas, endotracheal tube size, and method of connection of the delivery system to the ventilator circuit \cite{9}. Several authors reported that when the administration technique is carefully employed, aerosol delivery during mechanical ventilation is comparable to that in ambulatory patients \cite{10}.

There are two primary methods of aerosolized drug delivery during mechanical ventilation nebulization and inhalation \cite{e.g. dry powder inhalers or pressurized metered-dose inhalers (pMDIs)\}. Nebulized drug administration is mainly conducted by means of three types of nebulizer systems;
ultrasonic, jet and vibrating mesh–aperture plate. A nebulizer is powered by either a continuous oxygen source or pulse gas source depending on the mechanical ventilator used. It is connected to the inspiratory limb of the ventilator circuit and generates aerosol continuously, though it can be adapted to generate aerosol only during inspiration. During nebulization, external sources of humidification should be minimized. Main disadvantage of antibiotic delivery using nebulizers is the amount of drug wasted. Even with use of an optimal nebulizer, a proportion of the total dose is delivered to the lung. The rest of the dose is left in the dead space of the nebulizer or tubing, or it is released into the environment [11].

NEBULIZERS

In older ventilators, a nebulizer was connected to an oxygen or compressed-air gas source independent of the ventilator to deliver the antimicrobial agent. To provide adequate aerosol output, the oxygen or compressed-air was traditionally administered with airflow of 6-8 L/min. Newer ventilators offer an independent control for nebulizer use with obvious advantages. The advantages of the ventilator-powered nebulizer include less waste of drug administered and no distortion of mechanical ventilator readings, such as the sensitivity, triggering of the assisted breath, the delivered tidal volume or the minute volume. Several studies have been conducted during the past years to determine the suitability of various nebulizer devices [12, 13].

ULTRASONIC NEBULIZERS

Ultrasonic nebulizers produce an aerosol from the shear force created by a vibrating piezoelectric crystal. Nebulizer output is affected by the source and flow of gas used to carry the aerosol. Low flow rates yield smaller particles and higher concentrations of aerosol, whereas high flow rates yield larger particles and lower aerosol concentrations. This class of nebulizer produces the most consistent and efficient aerosol in patients receiving mechanical ventilation. Main characteristics are a quiet operation, higher mean output and shorter administration times (10 min versus 15-30 min of ultrasonic nebulizers) [14-16]. On the contrary, they have some major drawbacks, such as cost, maintenance problems, nebulization of solvent rather than active drug deposition of solution on canister walls, need to clean the unit after each use, and possible denaturation of active molecules during aerosolization [17]. All these disadvantages have resulted in limited application of ultrasonic nebulizers in the administration of antimicrobial agents by means of the respiratory route.

JET NEBULIZERS

Jet nebulizers produce an aerosol by forcing a compressed jet of gas over the medication solution. Drug vapor is generated when compressed gas is passed through a small hole to an adjacent reservoir containing the antibiotic solution. A volume of 4-6 ml of drug solution is necessary in jet nebulizers, while the recommended flow rate is 8 L/min [18].

There are two main types of jet nebulizers used in clinical practice: standard and breath enhanced. The breath-enhanced jet nebulizer system achieves better drug delivery to the lower airways during nebulization [19].

Main advantages of jet nebulizers are low cost, low requirements of special equipment and disposability. On the contrary, main disadvantage of jet nebulizers is inability of generating optimum particle size and the prolonged duration of nebulization to administer a specific dose.

VIBRATING MESH–APEXURE PLATE NEBULIZERS

It is new generation of nebulizer devices that uses a vibrating mesh or plate with multiple apertures to produce aerosolized particles [20]. This device produces a drug output is 2–3 times higher drug output compared with jet nebulizers. Main advantages include stable temperature of the antibiotic solution during nebulization and minimum risk of proteins’ denaturation. This device can be used in many types of ventilators without changing the settings and has been touted to provide advantages over traditional pneumatic or ultrasonic nebulizer delivery.

PRESSURIZED METERED-DOSE INHALERS (pMDIs)

A metered-dose inhaler (MDI) has several advantages over a nebulizer, such as lower cost, dose reliability, ease of administration, and lower risk of contamination. An MDI is actuated to synchronize with the onset of inspiratory flow of the volume- or pressure-controlled cycle breath to maximize aerosol dispersion and deposition into the lungs. A strategy has been recommended for aerosol delivery in patients receiving invasive mechanical ventilation. However, the optimal dose administered with an MDI for patients receiving mechanical ventilation remains unknown. Endotracheal instillation of MDI aerosol using a long catheter has been criticized since MDI constituents might damage bronchial mucosa [21].

Dry-powder inhalers (DPIs) are not routinely used in mechanically ventilated patients. They are small portable devices and have the advantage, in ambulatory patients, that they do not require coordination of actuation and inhalation. Main disadvantage of the device is that if the amount of medicine contained in the capsules or blisters used is not enough, repeated doses are required.

The greatest concern regarding the use of inhaled/aerosolized antibiotics, as with all antimicrobial agents regardless the administration route and/or technique, is the emergence of resistance. This is getting even more serious when the emergence of resistance occurs in the ICU environment. After prolonged administration of aerosolized antibiotics, the selection of drug-resistant pathogens such as methicillin-resistant Staphylococcus aureus is a possibility [22]. A greater concern is the potential for antibiotic contamination of the ICU environment, leading in selection of multidrug-resistant (MDR) Gram-negative pathogens. Because the potential for a substantial increase in resistance is large, measures such as the use of nebulizer exhaust circuit filters and ventilator nebulizers should be widely used, in order to minimize environmental contamination [23]. Patients with prolonged mechanical ventilation and prolonged administration of inhaled/aerosolized antibiotics should be monitored for antibi-
otic resistance for specific pathogens. Finally, strict adherence to infection control policies is required, in order to minimize transmission of resistant pathogens within the hospital environment.

Although data are not available concerning environmental contamination through use of inhaled antibiotics, local environmental contamination does not seem to be related with the antimicrobial agent used but with the aerosol technique. A further concern, for patients receiving antibiotics via the respiratory tract, is the potential for microbial contamination of the equipment used for drug delivery [24]. Adequate cleansing and drying should always take place and reuse of disposable equipment should be avoided, since it can lead to nebulization of microbes. Health centers, in order to minimize microbial contamination of the drug delivery equipment, should develop policies for aerosolized antibiotic in mechanically ventilated patients. The use of filters, the disposal of unused product and thorough cleaning of nebulizers are some examples.

NEWER DRUG FORMULATIONS, DEVICES AND PERSPECTIVES

There is ongoing research and development of antibiotics and associated devices, for pulmonary delivery. Newer formulations of currently used antibiotics are under study. They include, among others, liposomal and dry powder tobramycin [5] and aztreonam lysinate. These formulations have received an orphan drug designation by EMEA for use in CF patients.

Intra-tracheal aerosol inhalation of antimicrobial agents is a novel under study aerosol delivery technique for use during mechanical ventilation. Using an intra-tracheal catheter, medications are directly delivered to the lungs, optimizing that way therapeutic outcome. The AeroProbe Intracorporeal Nebulizing Catheter (Trudell Medical International, London, Ontario, Canada) has been experimentally used in vivo and in vitro [25,26].

Other newer devices, like vibrating mesh devices and adaptive aerosol delivery devices are currently off-label used in ambulatory CF patients for pulmonary delivery of antibiotics. Main advantages of the newer devices, over the traditionally used nebulizers, are the lesser time needed for delivery and the less quantity of wasted drug. Main disadvantage is their increased cost. Since the only formal indication of inhaled antimicrobial agents is in CF patients, the vast majority of information published, is about this group of patients. There are currently no data about the use, applicability and efficacy of these newer devices in mechanically ventilated patients. If these newer devices are found effective in mechanically ventilated patients, it would be of interested to examine their impact in the ICU environment. They could possibly lower treatment cost, if they decrease the workload of the ICU personnel and minimize the quantity of wasted drug. They could also be proving safer, compared to nebulizers, if they deliver greater amounts of antibiotic to the lungs and release less antibiotic to the ICU environment. But do these hypothetical advantages counterbalance their increased buying cost compared to MDIs and nebulizers? A well designed clinical trial may be the answer to these questions.

The success of aerosolized antimicrobial therapy depends on four major factors; the lung disease, the delivery system, the type and the specialized formulation (designed for aerosolized delivery) of the administered antimicrobial agent. Respiratory infections, such as purulent tracheobronchitis or infections on patients with cystic fibrosis or bronchiectasis, involving mainly the airways with no substantial systemic participation, maybe are more suitable candidates for aerosolized antimicrobial therapy compared to diseases involving the lung parenchyma (e.g. pneumonia). However, there are recent studies that report satisfactory results regarding the safety and efficacy of antibiotics (e.g. colistin) in patients with ventilator-associated pneumonia (VAP) due to multiderg-resistant Gram-negative pathogens [27]. On the other hand, it is known that jet and ultrasonic nebulizers and dry powder devices are effective if they produce particles of the antimicrobial agents targeting to the lower airways. The objective of the antibiotic aerosolized treatment in patients with VAP is obviously a high local peripheral concentration in the lung [28].

The delivery of aerosolized antimicrobial agents to the respiratory system during mechanical ventilation is optimized, if the target of deposition and the required antibiotic mass to be deposited are precisely defined. In addition, optimization of the deposition of the aerosolized antimicrobial agent means to precisely determine the most appropriate particle characteristics and breathing patterns to deliver the maximum therapeutic aerosolized agent to the tracheobronchial tree or the lung, taking into consideration that deposition in the non-targeted regions may cause side effects. Thus, to minimize deposition in other regions of the respiratory system is also part of the optimization procedure.

The deposition of an inhaled antimicrobial agent in the airways or alveoli occurs by means of three different mechanisms: sedimentation (when the droplets or particles are influenced by the force of gravity); inertial impaction (when a droplet impacts the airway wall); and diffusion (resulting in droplets’ collisions with the airway wall). In inertial impaction, larger particles with greater inertia deposit in the more proximal airways. In general, the smaller the particles, the more likely it is that they will reach the distal parts of the lung. The role of different deposition mechanisms depends on particle size and breathing parameters. The amount of the aerosolized antimicrobial agent that deposit is known as the deposition fraction. Obviously, the main goal of aerosolized therapy is to increase the deposition fraction targeting the deposition to smaller peripheral airways and alveoli in cases of VAP. Ventilators should administer the nebulized antimicrobial agent during inhalation with flow rates greater than 6 L/min, which improve lung deposition. Many factors influence total and regional deposition such as the underlying disease, age, and lung function. [29,30].

The deposition characteristics and efficiency of inhaled antimicrobial agents are largely dependent on aerosol particle size. Many factors may affect the nebulization rate and particle size distribution of a nebulizer. Among these are flow rate, initial volume of liquid, surface tension and composition of the liquid, humidity, and structural differences between models such as baffle design and jet orifice size [31].
The uptake of antimicrobial agent mainly depends on the size and surface properties of droplets. What is the optimum particle size? Droplets with a diameter above 5 μm are deposited in the oropharynx and upper airways. Droplets with a diameter of 3 to 5 μm have the greatest likelihood of being deposited in the tracheobronchial tree. Inhaled antimicrobial agents are delivered to the airways of patients with cystic fibrosis or bronchiectasis by means of devices that produce droplets of this size. On the contrary, other agents, such as aerosolized pentamidine or inhaled colistin, targeting the terminal bronchioles and alveoli, should produce smaller sizes of particles. [32,33] In general, the efficacy of delivery device in cases of VAP mainly depends on the production of smaller particle size [34].

The efficacy of an aerosolized antimicrobial agent can be affected by the delivery system and the interaction of the substance with the inhaled agent [35]. This may be particularly important for antibiotics, such as colistin. Aerosolized polymyxin E may result in surface tension lowering and foaming which can decrease the droplet size. New and potentially more effective inhalation devices have been recently developed to overcome this problem.

Sufficient therapeutic concentrations of the aerosolized antimicrobial agents are achieved deep in the respiratory tract at the site of infection with optimum administration techniques [36]. Aerosolized antibiotic delivery mainly depends on the applied administration technique [37].

DOSES OF INHALED ANTIBIOTICS

Several factors contribute to a highly variable pulmonary drug deposition. First of all, the devices have variable efficiency which may result in significant variations in the administered inhaled dose. Second, the physical properties of the administered antimicrobial agent may affect the inhalation process. Other significant factors are the type of respiratory disease and the inhalation technique.

The measurement of the dose of the inhaled agent to the lung is a difficult task. The deposition of an antimicrobial agent in the lung can be measured by gamma scintigraphy technique using a gamma camera [38]. This technique measures the total dose delivered to the lung at a certain time. It can also assess the regional distribution of deposited radioactive agent distinguishing extrapulmonary and pulmonary distribution, or the deposition in central airways or the lung periphery. Other alternatives to gamma scintigraphy quantifying the dose delivered to the respiratory system without measuring the regional distribution are filters or laser diffraction devices, placed near the patient’s mouth, can measure the drug delivered during inhalation and exhalation.

It should be emphasized that the optimal inhaled dose for almost all antibiotics is unknown. In order to reach the optimum dose, we may based on serum concentration levels obtained after antibiotic inhalation since it is considered to reflect pulmonary drug deposition, provided that no gastrointestinal absorption of the drug occurs, as in case of inhaled aminoglycosides and polymyxins. Another indirect method to estimate pulmonary antibiotic deposition is the measurement of drug concentration in the sputum of patient. However, it should be noted that the sputum PK analysis is less valuable compared to serum PK analysis, since it is affected by several patient dependent variables and disease specific factors [39]. In addition, sputum concentrations provide little information on the drug deposition in the deeper airways or alveoli.

Recently sufficient knowledge has been gained in the administration of inhaled aminoglycosides. Lung aminoglycoside concentrations of at least 10-40 μg/mL are needed in order to maximize the opportunity for a good outcome of a respiratory infection. However, it should be noted that none aminoglycoside administered systemically can achieve these lung concentrations [40] in contrast to the inhaled form of aminoglycosides [41] that can achieve concentrations in respiratory samples higher than 200 μg/mL [42].

CONCLUSIONS

During the last decade, several antimicrobial agents such as aminoglycosides, beta-lactams and polymyxins have been administered as aerosols as adjuvant treatment of VAP in critically ill patients, with no history of cystic fibrosis. Aerosol delivery of antimicrobial agents during mechanical ventilation is associated with multiple advantages such direct delivery of antibiotic to the respiratory tract, higher lung concentrations of the antimicrobial agent, faster onset of antimicrobial effect and less frequent and mild systemic adverse effects.

Many clinicians (especially intensivists) have obtained a valuable experience from the aerosolized administration of antibiotics and persuaded of their efficacy and safety. However, RCTs are needed to answer important clinical questions, such as what is the appropriate dose of antibiotic, the optimal delivery device, the optimal way of drug administration, as well as the exact therapeutic role of aerosolized administration of antimicrobial agents in the treatment of VAP.

REFERENCES
