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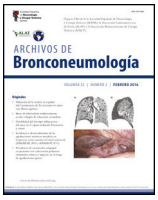

Editorial

Are inhalation devices important in antibiotic treatment?☆

¿Son importantes los dispositivos de inhalación en antibioterapia?

For years, the inhaled route has been considered a very attractive way to introduce different substances into the lung, since high concentrations can be reached with few side effects.[1] This approach has led to the development of inhaled antibiotic therapy, which has helped pulmonologists achieve control of many respiratory infections.

The effectiveness of inhaled drugs depends on both their formulation and the capacity of the device to deposit of appropriate doses in the lung.[2,3] Nebulizers, pressurized inhalers, and dry powder inhalers are available to deliver inhaled antibiotics and other substances.[2,4,5] When we talk about inhaled antibiotics, other specific factors must be borne in mind, such as molecular size, the logP/lipophilic ratio (the coefficient indicating the ease of diffusion by water), and the existence of receptor-mediated transport mechanisms.[3–6]

Various types of nebulizers are now available, but their pros and cons must be studied, especially if they are to be recommended for aerosolizing antibiotics. Ultrasonic devices ensure the nebulization of large amounts of fluids, but they can denature some drugs, such as antimicrobials, so in this case they are not recommended. Pneumatic or jet nebulizers (which include continuous flow with a Venturi effect, dosimetric, and modified release devices) are widely used for inhaled antibiotic therapy, particularly because many have been designed to be activated by inspiration and lose less volume into the environment. Mesh nebulizers (static or vibrating) are a more recent innovation. They are silent and fast, and some even also feature modified release mechanisms.[5,7,8] A major problem is the cleaning of these devices[7]: inadequate cleaning can lead to infection.

The wide variability in the amount of drug administered by inhaled therapy devices has only recently been understood.[2] Many of the studies with inhaled antibiotics were performed with jet nebulizers, and we do not know if the same doses are delivered by mesh devices, so these latter need to be dose-adjusted and not simply adopted into clinical practice. Therefore, when we recommend an inhaled antibiotic, we should consider not only the antimicrobial spectrum and the characteristics of the medication to be inhaled, but also the best device for obtaining an optimal deposit in the lung.

Research into inhaled antibiotics has a promising present and future, and many of our needs in the treatment of lung infections have been or will soon be met. The new formulations are also marketed with a specific device, so we must be familiar with not only the characteristics of the antibiotic selected, but also the features of the accompanying device. However, it is inconvenient for patients to keep a series of different instruments at home to aerosolize their drugs. Everyone's goal, of course, is to achieve better lung deposits, but we should ask whether this can be achieved with a universal nebulizer/compressor, to avoid complicating the already difficult lives of our patients with bronchial infections.

New technologies allow the administration of dry powder inhaled antibiotics, and this is clearly the future for these treatments. Dry powder inhalers use powder specifically designed for this purpose, supplied in a hard capsule containing the medication and delivered via the specific inhalation device.[2] Several techniques are used to produce these particles, the most advanced being spray drying.[2] PulmoSphere® technology has succeeded in producing spherical, porous and uniform particles, while various devices have been developed that offer low resistance to air flow, facilitating the dispersion and deposit of dry powder (Podhaler®, Cyclops® and Orbital®).[2,6,9] So far, we have only 2 dry-powder antimicrobial drugs in our portfolio: tobramycin (TIP-Podhaler®), which has not secured funding, and sodium cholistimethate (Colobreathe®). This is clearly the future for inhaled antibiotic therapy, but its use is currently associated with some setbacks, which must be remedied over time. The first dry powder antibiotics needed high numbers of capsules to be inhaled to achieve the right dose, requiring patients to spend as much time on the process as they would have spent on nebulization. In addition, inhalation causes coughing attacks in many patients, leading to dropouts; slow and repeated inhalations are recommended to avoid coughing, but this also takes some time. On the other hand, these devices are easier to transport, manage, and clean.

Nebulization solutions have evolved in recent years, and surfactant has been added for improved lung deposition and antimicrobial efficacy.[6] Liposomal or encapsulated formulations have led to the development of controlled and maintained release of particles with improved biofilm penetration.[2,6,7,10]

A promising strategy in this respect are nanoparticles, which can penetrate the aqueous pores of the thick mucus barrier that prevents antibiotics from reaching bacterial colonies located in the lung.[11–13] Some groups are also developing alternative formulations of antibiotic nanoparticles called complex nanoparticles (nanoplexes) or polymeric nanoparticles.[2,11] Despite their small size, nanoparticles can be deposited in the alveolar space by sedimentation, due to their accumulation in the lung. Polymeric

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nanoparticles can also persist in tracheobronchial secretions for long periods of time, which is particularly advantageous in the case of antibiotic formulations.[2] If we compare their properties with those of liposomal antibiotics, we find that liposomes are slightly more permeable, although nanoplexes have a faster dissolution and a higher useful pharmacological payload, so fewer doses are needed to obtain the same result; although they have similar antimicrobial activity, they are especially susceptible to mucociliary clearance and phagocytosis.[2,11,12]

In the future, new inhaled antibiotics, pharmacological combinations and long-release formulations will become available for the control of multidrug-resistant infections, including tuberculosis, while avoiding side effects.[9,14] We will have to wait to know the harmful effects of prolonged persistence of these molecules in the lung tissues.

Conflict of interests

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