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Editorial

Nebulized Antibiotic Therapy☆

Tratamiento antibiótico nebulizado

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Medical practice is probably based on 3 pillars: the skill of the physician, scientific evidence and common sense. The first pillar relies on the experience, talent and passion of the professional; the second on the evidence provided by nature from which, after analysis, valid conclusions applicable to most individuals can be drawn; and the third, on mankind's power of reasoning, gained over years of evolution. This last pillar is of particular importance in situations where skill and evidence do not suffice, but decisions must be made.

Common sense dictates that the most effective way to treat diseases of the airway must be inhalers or nebulizers. Based on this premise, the introduction of bronchodilators and inhaled corticosteroids revolutionized the treatment of asthma and COPD, forever changing the history of the disease and the lives of individual sufferers. It is surprising to note, however, that further advances of this magnitude have not been made with other products.

Antibiotics are currently among the most commonly used therapies for respiratory infections, and are usually used systemically despite the localized nature of the infection. Studies to date, however, have consistently shown that inhaled or nebulized antibiotics increase drug concentrations at the infection site, thereby reducing the number of systemic adverse effects.[1,2] As a result, antibiotics specifically prepared for administration with nebulizers have appeared on the market, such as colistin, tobramycin or aztreonam, which are indicated for use in cases of chronic *Pseudomonas aeruginosa* (PA) infection in patients with cystic fibrosis (CF).

From a scientific point of view, particularly with respect to non-CF bronchiectasis, much remains to be accomplished. However, it is generally felt that in most cases these products are effective when given to the right patient, a hypothesis that has been substantiated by the results of many studies.[3,4] It has taken many years for the number of diagnoses of bronchiectasis to lead to clinical trials large enough to provide greater scientific evidence. In 2013, the AIR-BX1 and AIR-BX2[5] studies evaluated the efficacy of inhaled aztreonam lysine versus placebo in patients with bronchiectasis and chronic bronchial infection caused by any Gram negative bacteria except for *Haemophilus influenzae*. The study concluded that aztreonam was not superior in either the primary endpoint (changes in quality of life) or in most secondary variables, while an increased number of adverse effects were observed in the treatment group. The PROMIS[6] study, meanwhile, evaluated the efficacy of colistimethate sodium delivered through the I-neb® device in 144 patients with bronchiectasis and chronic PA infection. In this study, the intention-to-treat (ITT) analysis revealed no statistically significant difference in the primary endpoint (time to first exacerbation), although the difference between groups was 54 days. However, improvements in quality of life parameters and a reduction in PA density were observed, and when analyzing the subgroup of patients with good adherence to treatment, the effect of the active ingredient on the main endpoint was found to be statistically significant (168 vs 103 days; P=.028) with no increase in adverse effects.

What conclusions can be drawn from the results of these two studies? In the AIR-BX1 and AIR-BX2 studies, the negative results may be due to the inclusion of patients with chronic bronchial infection caused by Gram negative bacteria other than PA, given the particular virulence of this microorganism.[7,8] In this sense, analysis of the subgroup of patients with chronic PA bronchial infection could give more promising results, and form the basis for other clinical trials. As for the PROMISE study, the sample size was most probably too low to demonstrate a statistically significant difference in the primary endpoint, although 54 days is a clinically significant difference. These results should be confirmed in a larger clinical trial to ascertain the true potential of colistin in the treatment of these patients. Finally, this study clearly shows the need for monitoring adherence to treatment with inhaled antibiotics.

Despite the mixed results and questionable methodologies used in studies to date, the future of inhaled antibiotics is still promising. Many pharmaceutical companies have already started randomized phase III clinical trials with different inhaled or nebulized antibiotics such as colistimethate sodium, tobramycin, aztreonam lysine, ciprofloxacin, levofloxacin, vancomycin and amikacin, among others. In most cases, these products have already successfully passed the preclinical safety, efficacy and optimal dose determination phases. Another interesting field of study is the effect of inhaled antibiotics on other acute or chronic airway infections such as COPD with chronic bronchial infection, sinusitis or pneumonia. There is no reason for discouragement, therefore, as everything seems to indicate that, as is often the case in medicine, logic and common

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sense are way ahead of scientific evidence, and in the words of Albert Einstein: "if the facts don't fit the theory, change the facts". The time has come to revise the old facts and methods and generate new ones in the hope that inhaled or nebulized antibiotics will be effective in resolving airway infections and improving the quality of life of our patients, and who knows, we may be on the brink of a breakthrough similar to that of the1970s when inhaled bronchodilators and corticosteroids changed the lives of patients with asthma and COPD forever. Until then, returning to the opening statement of this editorial, at least in the field of bronchiectasis the skill of the physician and common sense prevail over scientific evidence.

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