Inhaled gentamicin in non-cystic fibrosis bronchiectasis: effects of long-term therapy


Sabina A Antoniu† & Antigona Carmen Trofor†
University of Medicine and Pharmacy “Gr.T.Popa” Iasi, Pulmonary Disease University Hospital, Department of Medicine II – Pulmonary Disease, Iasi, Romania

Bronchiectasis is a disease state defined by irreducible dilations of the airways. If they occur in diseases other than cystic fibrosis they are termed non-CF bronchiectasis. The common denominator is the increased risk of recurrent infections with bacteria, such as Staphylococcus aureus or Pseudomonas aeruginosa. Such infections are difficult to eradicate with systemic antibiotics because the structural abnormalities in the bronchial wall reduce their bactericidal effect at this level. An alternative to systemic antibiotics might be represented by inhaled formulations, which can be given in much lower doses and can be more effective. Previous studies demonstrated that inhaled gentamicin can reduce bacterial load and local infection in both cystic fibrosis and non-CF bronchiectasis. The study discussed in this paper demonstrates that long-term therapy with inhaled gentamicin can eradicate the infection or reduce the bacterial load, decrease the risk of subsequent infections and improve the quality of life in patients with non-CF bronchiectasis with a minimal risk of side effects.

Keywords: antibiotics, bacterial infection, bronchiectasis, gentamicin, inhaled antibiotics

1. Introduction

Bronchiectasis can be defined as irreducible dilations of the bronchi and are caused by alterations of their normal structure [1]. Bronchiectasis can have various causes and are a common finding in cystic fibrosis or in other chronic diseases (non-cystic fibrosis bronchiectasis). Irrespective of the underlying cause, bronchiectasis manifest with symptoms such as chronic cough, sputum production and recurrent infections [1]. The latter are risk factors to chronic colonization of the airways especially in the more advanced disease, the bronchial persistent inflammation and the structural abnormalities present at the bronchial level being predisposing factors.

Currently, bronchiectasis is diagnosed with high resolution computed tomography (HRCT) which has replaced the contrast bronchography traditionally used as a golden standard method to diagnose this condition.

Non cystic fibrosis (non-CF) bronchiectasis can occur due to various diseases such as airways infections, sarcoidosis, allergic bronchopulmonary aspergillosis (ABPA) or immune deficiencies [2].

Apart from respiratory symptoms, which can occur intermittently or continuously, lung function loss is also another hallmark of the disease including non-CF subset. Lung function loss is accelerated not only by the presence of chronic airways...
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Inflammation but also indirectly by the chronic colonization with various bacteria such as Staphylococcus aureus, Haemophilus influenzae or Pseudomonas aeruginosa.

Various therapeutic methods are used to treat non-CF bronchiectasis and antibiotic therapy has a prominent role in treating infectious exacerbations and preventing/treating chronic colonization. Most of the antibiotics are currently given systemically but inhaled formulations have already started to demonstrate their efficacy: inhaled tobramycin or inhaled colistin were demonstrated to be efficacious in treating P. aeruginosa infections in cystic fibrosis as well as in non-CF bronchiectasis [3,4].

Gentamicin has also been emerged as a potential inhaled therapy in bronchiectasis. This paper discusses the results of a recent paper analyzing the effects of long-term therapy in adults with non-CF bronchiectasis [5].

2. Methods and results

This was a randomised placebo-controlled study evaluating the efficacy and safety of 12 months therapy with nebulised gentamicin 80 mg twice daily and of placebo (normal saline) 5 ml nebulised twice daily in patients with non-cystic fibrosis bronchiectasis [5,6]. Included were patients with non-cystic fibrosis bronchiectasis, with chronically infected sputum, at least two exacerbations in the previous year, ability to tolerate the nebulised gentamicin, FEV1%pred > 30% predicted, ex-smokers of more than 1 year, with clinically stable disease at the time of enrolment, no long-term antibiotic therapy. Primary outcome was represented by ≥ 1 log unit reduction in sputum bacterial density whereas secondary outcomes were qualitative sputum bacteriology, the identification of new strains of gentamicin-resistant Pseudomonas aeruginosa, markers of airways inflammation in sputum, sputum production over 24 h, sputum purulence, lung function, exercise capacity, health-related quality of life, systemic inflammation, exacerbations and side effects. Adherence to the inhaled therapy was also measured [6].

There were 65 patients enrolled in the study, 32 in the treatment group and 33 in the placebo group. A total of 57 patients completed the study 27 patients in the treatment group and 30 in placebo group. There were two unexpected deaths in the treatment group (one due to colorectal cancer and one due to myocardial infarction). There were six withdrawals three in each group. The median age was 58 in the treatment group and 64 in the placebo group, there were 9 males in the treatment group and 15 in the placebo group, most of the patients in both groups were taking inhaled corticosteroids, rescue bronchodilators and long-acting β2 agonists. In terms of etiology of bronchiectasis, the predominant etiology in both groups was post-infective (40.7% in the treatment group and 36.7% in the placebo group respectively) followed by idiopathic (29.6% in the treatment and 30% in placebo group respectively). The bacterial strain the most commonly detected in both groups was H. influenzae in placebo group 50% and P. aeruginosa in treatment group 48.1% [6].

At baseline the bacterial load was comparable in both groups (8.02(7.63 – 8.3))log10 CFU/ml in the treatment group and (7.88(7.34 – 8.17))log10 CFU/ml. Inhaled gentamicin resulted in its significant reduction (2.96(1.0 – 5.9))log10 CFU/ml versus (7.67(6.46 – 8.19))log10 CFU/ml in placebo group, p < 0.0001. Three month after stopping inhaled gentamicin, the bacterial load returned to levels comparable between the groups and with baseline. Eradication of bacterial infection was obtained in 92.8% (13 in 14 patients) of the patients in the treatment group infected at baseline with strains other than P. aeruginosa, whereas in the P. aeruginosa group this was obtained in 30.8% (4 of the 13 patients). In patients in whom eradication was not obtained the bacterial load was however maintained at a significantly lower level as compared to baseline. No gentamicin resistant strains of P. aeruginosa were detected at the end of the study. Inhaled gentamicin therapy reduced significantly the levels of sputum biomarkers of airways inflammation. Sputum purulence at the end of the treatment and three months afterwards were comparable. Sputum volume and lung function were not influenced by gentamicin throughout the study period. Exercise capacity and health-related quality of life improved significantly more in the inhaled gentamicin group. Systemic inflammation was reduced transiently with gentamicin therapy. The number of exacerbations was also found to be significantly reduced in the treatment group (0 versus 1.5, p < 0.0001) and in the same group the proportion of patients with one exacerbation during the study period was 33.3% compared to 80% (p = 0.005). The time to first exacerbation was significantly prolonged as compared to placebo (120 days versus 61.5 days, p = 0.02). Only one patient developed serum gentamicin of > 1 mg/ml and this decreased after reduction of the dosage to once daily. Bronchospasm occurred in 21.9% of the patients in the treatment group and in 6% in placebo group. No nephro- or ototoxicity was reported. A suboptimal compliance level of 67.9% was detected only in one patient.

3. Significance of the results

This study demonstrates that in patients with non-CF bronchiectasis having chronic bacterial infection, inhaled gentamicin, given on long-term basis was able to eradicate the infection or to reduce the bacterial load, and thus to reduce the risk of subsequent exacerbations. This was associated with a reduction in airways inflammation and with an increase in exercise capacity and in health-related quality of life.

These data resulting from a study with appropriate design, duration and endpoints highlight the potential role of inhaled gentamicin, a relatively cheap antibiotic, in prevention of subsequent infectious exacerbations in adults with non-CF bronchiectasis.
The use of inhaled gentamicin in this setting is also supported by its ability to achieve high concentrations in sputum as compared to systemic formulation and to reduce P. aeruginosa load in the airways [7]. Inhaled gentamicin was also found to reduce significantly airways inflammation (assessed with the levels of sputum myeloperoxidase) and mucus hypersecretion as compared to nebulised normal saline. These effects were accompanied by a reduction in sputum volume, and by improvements in lung function, dyspnea level and exercise capacity [8].

4. Expert opinion

In bronchiectasis of various etiologies, the chronic airways colonization with various bacteria is favoured by the impaired local defence mechanisms. Among the bacterial strains most commonly detected were S. aureus, H. influenzae or P. aeruginosa. This chronic colonization increases the risk of recurrent infections and represents a major therapeutic challenge especially in the case of P. aeruginosa which is among the few bacterial strains the most difficult to eradicate.

Currently available options of antibiotic therapy include systemic or inhaled compounds. The former category is still the most widely used and includes various antibiotic classes among which commonly used are the aminoglycosides due to their broader antibacterial spectrum and to its strong bactericidal effects on P. aeruginosa. However, eradication of P. aeruginosa at bronchial level requires high doses and longer courses of aminoglycoside antibiotics and the beneficial effect of bacterial clearance could be associated with occurrence of side effects such as nephrotoxicity.

Furthermore, the structural abnormalities in the bronchial wall represent a barrier against antibiotic penetrability at bronchial level and therefore lower concentrations of drug are available despite high systemic dosage.

These inconveniences can be solved with topic administration of aminoglycosides, and tobramycin for dry powder inhalation is already authorized to treat P. aeruginosa in patients with cystic fibrosis.

The main advantage of using inhaled aminoglycosides is the high concentrations which can be achieved at bronchial level with minimal systemic exposure and with minimal risk of side effects especially if chronic administration is contemplated.

However, administration of inhaled gentamicin is sometimes associated with development of bronchospasm which might be due to the active substance or to the excipients. This can be rapidly relieved with inhaled β2 agonist bronchodilators but other preventive methods might be also required.

The eradicating effect of inhaled gentamicin against P. aeruginosa might be modest, but reduction of bacterial load at bronchial level might also result in the reduction of number of exacerbations.

Based on increased bactericidal efficacy of the inhaled formulation of gentamicin, it can be concluded that it can be used on long-term basis to prevent exacerbations in patients with bronchiectasis and chronic bacterial colonization.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.
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Bibliography


Affiliation
Sabina A Antoniu†1 MD PhD & Antigona Carmen Trofor2 MD PhD
†Author for correspondence
1Assistant Lecturer, University of Medicine and Pharmacy “Gr.T.Popa” Iasi, Pulmonary Disease University Hospital, Department of Medicine II – Pulmonary Disease, 30 Dr I Cihac Str, 700115 Iasi, Romania
Tel: +0040232239408;
E-mail: Sabina.antonela.antoniu@pneum.umfiasi.ro
2Associate Professor, University of Medicine and Pharmacy “Gr.T.Popa” Iasi, Pulmonary Disease University Hospital, Faculty of Dental Medicine – Pulmonary Disease, 30 Dr I Cihac Str, 700115 Iasi, Romania