Inhaled antibiotic therapy in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa*

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The aim of this study was to investigate the long-term effectiveness and safety of inhaled antibiotic treatment in non-cystic fibrosis patients with bronchiectasis and chronic infection by *Pseudomonas aeruginosa*, after standard endovenous and oral therapy for long-term control of the infection had failed. After completing a 2-week endovenous antibiotic treatment to stabilize respiratory status, 17 patients were randomly allocated to a 12-month treatment either with inhaled ceftazidime and tobramycin (group A) or a symptomatic treatment (group B). One patient from group A abandoned inhaled treatment because of bronchospasm and another from group B died before the end of the study. The remaining 15 patients, seven from group A and eight from group B, completed the study. Both groups had similar previous characteristics. The number of admissions and days of admission (mean ± SEM) of group A [0.6 (1.5) and 13.1 (34.8)] were lower than those of group B [2.5 (2.1) and 57.9 (41.8)] (P<0.05). Forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV1), Pao2 and Paco2 were similar in the two groups at the end of follow-up, showing a comparable decline in these parameters. There were no significant differences either in the use of oral antibiotics or in the frequency of emergence of antibiotic-resistant bacteria between groups. Microbiological studies suggested that several patients had different *Pseudomonas aeruginosa* strains. None of the patients presented impaired renal or auditory function at the end of the study. This study suggests that long-term inhaled antibiotic therapy may be safe and lessen disease severity in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa* which do not respond satisfactorily to antibiotics administered via other routes.

**Introduction**

In patients with cystic fibrosis (CF), *Pseudomonas aeruginosa* (PA) bronchial infection, once established, is rarely eliminated, leading to chronic bronchial infection by PA (CBIPA), a well-known complication in these patients (1). The change of PA to the mucoid phenotype may be associated with deterioration in lung function and an increase in morbidity and mortality, even though the patient is receiving standard oral or endovenous treatment (2).

Since the first study by Hodson (3), several peer-reviewed reports (4-13) have evaluated the efficacy of inhaled antibiotic therapy in the evolution of patients with CF and CBIPA. A significant beneficial effect of inhaled antibiotic therapy, implying fewer hospital admissions owing to respiratory exacerbation (4,8) and less respiratory function impairment, (3,7-9,12,13) has been demonstrated. A recent study (14), in which a meta-analysis was applied to integrate the results of randomized controlled trials, really established that treatment may reduce pulmonary exacerbations and improve spirometric lung function.

In patients with non-CF-based bronchiectasis, Nicotra *et al.* (15) showed PA to be cultured in almost 31% and the most frequent micro-organism in sputum. Wilson *et al.* (16) stated that all 22 non-CF bronchiectatic patients from whom a PA culture was obtained on an exacerbation-free day were chronically infected with the bacterium and had more hospital admissions and worse health-related quality of life than other bronchiectatic patients. Furthermore, CBIPA in non-CF patients with bronchiectasis has been associated with extensive lung disease and severe lung...
obstruction (16,17) and, recently, a rapid decline in lung function (18). Thus, CBIPA in this population could be more frequent and significant than generally supposed. It has been suggested (19) that long-term nebulised antibiotics should be considered in these patients when antibiotics by other routes would have been unsuccessful. However, there are no clinical trial data to support the benefits of this therapy (20).

The purpose of our study was to ascertain the long-term efficacy of home-inhaled antibiotic therapy in the outcome of non-CF patients with bronchiectasis and CBIPA who fail to respond satisfactorily to antibiotics by other routes.

Material and Methods

PATIENTS

Between 1993 and 1994, 17 patients who met the conditions stated below were enrolled at two university centres. All patients had a diagnosis of bronchiectasis confirmed by bronchography, thoracic computed axial tomography, or both. Two sweat tests were normal in all cases. Blood samples were all negative for 31 CF mutations, including AF508, G542X and N1303K, the most frequent mutations in Spain (21). A study was carried out to ensure that immunodeficiency, enzymatic deficiency and congenital disease were not the cause of the bronchiectasis. Four patients had had tuberculosis, and two whooping cough in infancy. Patients had been treated at our hospitals for almost 2 years before they entered the study owing to respiratory exacerbations and because they had been difficult to control in the long term. PA had been grown consistently from the sputum. At least three positive cultures during the year prior to entering the study were obtained in each patient. No other pathogens were found in the sputum samples at the beginning of the trial. The patients had been treated at least once with ciprofloxacin p.o. (500 mg every 12 h for 3 weeks) in the last 3 months because of exacerbation without recovery or with relapse of symptoms. Patients with β-lactam or aminoglycoside hypersensitivity or bacterial resistance in the antibiogram and those with kidney failure were excluded from the study.

The study was approved by the ethics committee of each centre. All patients provided informed consent.

STUDY

This was a pilot, prospective, randomized, non-blinded trial. Patients were admitted owing to failure to recover from respiratory exacerbation or relapse of symptoms. Appropriate symptomatic treatment was then administered, including oxygen, bronchodilators and corticosteroids. All patients completed a routine 2-week endovenous antibiotic treatment (ceftazidime 100 mg kg⁻¹ day⁻¹; tobramycin 4 mg kg⁻¹ day⁻¹) following the standard protocol of our hospitals until their respiratory status was stabilised. Patients were then randomly allocated to a 12-month treatment either with the same two antibiotics by inhalation route (ceftazidime 1000 mg 12 h⁻¹; tobramycin 100 mg 12 h⁻¹) in group A or a symptomatic treatment in group B. All nebulised antibiotics were diluted in physiological saline to form a solution of approximately 8 ml. The solutions were administered separately twice a day using a jet nebuliser (System 22 Acorn, Medic-Aid, U.K.) driven by high flow-rate compressor (CR60, Medic-Aid, U.K.). This combination has proved useful for the nebulisation of antibiotics (22). Recent requirements established by the British Thoracic Society were also fulfilled (20).

Patients attended the outpatient clinic at the start of the study, during weeks 2, 4 and 8 and later during months 4, 6, 9 and 12. At each visit clinical history was recorded, patients were physically examined and asked about their treatment compliance and adverse effects. Chest X-ray, blood analysis, spirometry, arterial gasometry and sputum cultures were performed at months 1, 6 and 12. Audiometry was performed at the end of the study.

Supplementary use of oral antibiotics was permitted if a patient had an exacerbation, defined as more frequent coughing, more dyspnoea and an increase in sputum volume and purulence (23). The decision on hospital admission was taken by an A&E physician who was unaware of the study. Patients were treated in each new admission with the same antibiotic regimen used in the first. In accordance with the standard protocol of our hospitals, the endovenous antibiotic treatment was only changed if there was also clinical impairment in addition to bacterial resistance demonstrated by the antibiogram. Ceftazidime was replaced by piperacillin (200 mg kg⁻¹ day⁻¹) and tobramycin by amikacine (15 mg kg⁻¹ day⁻¹). The decision on hospital discharge was also taken by a physician who was unaware of the study. If an endovenous antibiotic had been changed on admission, antibiotic inhaled at home was also changed. Ceftazidime was replaced by piperacillin (100 mg 12 h⁻¹) and tobramycin by amikacine (100 mg 12 h⁻¹).

Microbiological study of sputum was performed if the latter fulfilled determined quality criteria on microscopic examination (24). The study included: Gram smear, conventional culture by standard microbiological loop in blood agar and McConkey media and quantitative culture by 0-001 ml calibrated loop with a previous dilution in 1 ml of sterile distilled water in chocolate agar. The threshold for detecting bacteria was 10⁶ colony-forming units (cfu ml⁻¹) in chocolate agar, but was lower in blood agar and McConkey media. PA was identified by conventional microbiology methods and the AMS Vitek (Bio Merieux, Marcy-Etoile, France) system. The antibiogram was carried out with an automated system Aladin (Ditasa, New York, U.S.A.) of microdilution in broth. The PA strains of 13 patients of one of the hospitals were serotyped and phagotyped in the National Microbiology Laboratory of Majadahonda (Madrid) [serotype by the IATS rules (25) and phagotype by the set CPHL (26)].

End-points studied were the number of hospital admissions, the number of hospitalization days, oral antibiotic use, forced vital capacity (FVC), forced expiratory volume in 1 sec (FV₁), $\text{P}_{\text{A}}\text{O}_2$, $\text{P}_{\text{A}}\text{CO}_2$, drug toxicity and the emergence of bacterial resistance.
TABLE 1. Characteristics of the study population (group A: inhaled; group B: non-inhaled) at enrolment

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=7)</th>
<th>Group B (n=8)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men/women</td>
<td>6/1</td>
<td>4/4</td>
<td>n.s.</td>
</tr>
<tr>
<td>Age (years)*</td>
<td>62.0 (8.5)</td>
<td>61.4 (10.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Bronchiectatic lobes*</td>
<td>4.0 (1.5)</td>
<td>3.0 (1.3)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Previous PA infection (days)*†</td>
<td>711 (609.7)</td>
<td>299.9 (446.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Admissions 2 years prior to study*</td>
<td>2.3 (0.9)</td>
<td>2.1 (1.1)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Admissions 1 year prior to study*</td>
<td>2.1 (1.1)</td>
<td>2 (0.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Last sputum (cfu ml⁻¹)*‡</td>
<td>&gt;10⁷ (0)</td>
<td>&gt;10⁷ (0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>FVC (ml⁻¹)*</td>
<td>1850 (1016)</td>
<td>1696 (597)</td>
<td>n.s.</td>
</tr>
<tr>
<td>FEV₁ (ml⁻¹)*</td>
<td>1037 (386)</td>
<td>866 (225)</td>
<td>n.s.</td>
</tr>
<tr>
<td>FEV₁ (% pred.)*</td>
<td>62.3 (19.9)</td>
<td>56.2 (21.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>P_{A}O₂ (mmHg)*</td>
<td>69.0 (8.2)</td>
<td>63.4 (12.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>P_{A}CO₂ (mmHg)*</td>
<td>41.3 (7.4)</td>
<td>42.5 (5.3)</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*Values are means ± SEM.
†PA: Pseudomonas aeruginosa.
‡Expressed in colony-forming units per ml of sputum.

n.s., not significant.

STATISTICAL ANALYSIS

Comparability of the treatment groups was assessed by Fisher’s exact test in the case of proportions and the Mann–Whitney U- or Wilcoxon test in the case of continuous variables.

Results

Seventeen patients were initially included. One patient from group A, who had severe bronchial hyperactivity, abandoned inhaled treatment because of bronchospasm, despite receiving intense bronchodilator treatment. Another patient from group B died of respiratory failure at 300 days of follow-up. The remaining 15 patients, seven from group A and eight from group B, completed the study. Both groups had similar previous characteristics (Table 1). When admissions 2 years and 1 year before the study were compared, the means were similar in the two groups.

The number of admissions (mean ± SEM) was lower (P<0.05) in group A [0-6 (1.5)] than in group B [2.5 (2.1)]. Also, the days of admission (mean ± SEM) were lower (P<0.05) in group A [13.1 (45.8)] than in group B [57.9 (41.8)] (Table 2). Only one patient from group A required admission, on four occasions. The remaining patients in this group were not admitted. In contrast, all patients except one from group B required admission. There was no significant difference in the use of oral antibiotics between groups.

FVC, FEV₁, P_{A}O₂ and P_{A}CO₂ were similar in the two groups at the end of follow-up. Decline of these pulmonary function parameters was similar in both groups. Microscopic study of sputum samples in both patient groups revealed the presence of abundant Gram-negative bacilli accompanied, in most cases, by Gram-positive cocci, mainly streptococci. PA was cultured in all samples from all patients. During follow-up, and in addition to PA, in two patients (one from each group studied) Streptococcus pneumoniae were isolated in some samples in one and Haemophilus influenzae in the other. No other bacteria or yeasts were detected. Three patients, two of whom belonged to group A, presented transient negative PA in sputum culture for more than 3 months. However, in the last sputum culture performed all patients of both groups presented abundant PA colonies. One patient from group A who did not receive endovenous antibiotics presented resistance to tobramycin in the antibiogram, with no clinical worsening. PA remained sensitive to ceftazidime and tobramycin in the other patients of this group. Four patients from group B developed resistance to ceftazidime, although in two of them this was only observed on a single antibiogram. Resistance to tobramycin was observed at the same time in one of these four patients. In three of these patients, the bitherapy administered was modified since the change in sensitivity to the antibiotic was accompanied by clinical worsening. PA serotypes and phagotypes were investigated in 13 patients: 75.7% of strains were sero-typable, with serotypes 011 (53.8%), 010 and 015 (38.5%) and 01-03 (23-1%) predominating, and 64-3% of isolates were phagotypable. It was notable that all but five patients had different PA strains. None of the patients presented impaired renal or auditory function at the end of the study.

Discussion

In CF, the genetic defect favours bronchial wall injury and permits early CBIPA. Thus, nearly 98% of the CF population is colonized after 10-14 years (27). CBIPA in non-CF patients with bronchiectasis seems to occur in older patients,
as in our series, when severe lung disease, a possible predisposing factor for CBIPA, has developed (16-18).

The results of this study show that long-term inhaled antibiotic therapy influenced severity of the illness in non-CF patients with bronchiectasis and CBIPA. This therapy decreased the number of hospital admissions and admission days. These findings are consistent with previous reports in CF patients (4,8). The use of placebo was not considered for different reasons: firstly, because of the difficulty in adequately matching for all the distinctive characteristics of the inhaled antibiotics used in the study; secondly, it was considered difficult to administer a placebo over such a long period of time; and finally, exactly how a nebulised placebo can influence long-term outcome remains unknown. In fact, it has been suggested (28) that a negative effect of the placebo on lung function in one of the best designed studies (13) cannot be ruled out. In the present study, both groups were controlled equally during follow-up, and the decision to admit and discharge patients was taken by physicians not participating in the study. Thus, it is unlikely that the lack of placebo may have influenced those end-points. Moreover, the fact that the number of admissions 2 years and 1 year before the study were similar supports our results. Moreover, the fact that the number of admissions 2 years and 1 year before the study were similar supports our results.

Several peer-reviewed reports in CF patients have found improvement in lung function after aerosolized antibiotics (3,7,9,12,13). Contrary to these studies, the inhaled antibiotic therapy in our study was not associated with an improvement in lung function. However, only one of the positive studies mentioned had a duration longer than 6 months (12), whereas our patients were treated for 12 months. This longer study period could have had an influence, as a decline in the efficacy of inhaled antibiotic therapy in lung function when administered for more than 28 days has been described (11,13). In fact, significant differences in lung function were not observed in three (4,5,10) out of four reports (4,5,10,12) of CF patients with a follow-up longer than 6 months. Moreover, our patients, whose progress may differ from CF, had severe irreversible lung disease and low function at enrolment which may have made it difficult to establish any improvement in lung function after inhaled therapy.

Due to the rarity of this condition numbers of patients are low and therefore a cross-over design could have been a possible option. However, the present study lasted for 12 months, during which time the characteristics of the patients may have changed, therefore this type of design could potentially have been flawed (29).

Despite the severe chronic bronchial obstruction seen in our patients, long-term administration of inhaled antibiotics appears to be safe. Bronchoconstriction excluded one patient from the study, but did not occur in any others. Although risk associated with tobramycin inhalations is possible, due to unpredictable systemic absorption, in our study patients' renal and auditory measurements remained within the normal range. The resistance of PA to inhaled antibiotics has been a matter of controversy. Most reports on CF show no further emergence of antibiotic-resistant PA strains (3,5,7,13). However, inhaled therapy in these studies was only used for short periods of time. The effect of long-term administration is not well known. In our 12-month study, the frequency of emergence of PA-resistant organisms was no higher in patients with inhaled therapy than in the other group. Moreover, it was only necessary to change the endovenous antibiotics owing to bacterial resistance and poor clinical response in patients without inhaled antibiotics. This criterion was taken into account as current microbiological evidence separates the development of in vitro pseudomonal resistance from adverse clinical outcome in CF with CBIPA (14). The fact that several patients in our study had different PA strains might also have influenced our decision to change the antibiotics if there was clinical impairment.

Table 2. Summary of group changes (group A: inhaled; group B: non-inhaled) during follow-up

<table>
<thead>
<tr>
<th></th>
<th>Group A (n=7)</th>
<th>Group B (n=8)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of admissions</td>
<td>0.6 (1.5)</td>
<td>2.5 (2.1)</td>
<td>0.023</td>
</tr>
<tr>
<td>(mean)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days of admission</td>
<td>13.1 (34.8)</td>
<td>57.9 (41.8)</td>
<td>0.033</td>
</tr>
<tr>
<td>(mean)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral antibiotic use</td>
<td>1.1 (1.2)</td>
<td>4.0 (4.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>FVC (ml⁻¹)*</td>
<td>1655 (839)</td>
<td>1466 (355)</td>
<td>n.s.</td>
</tr>
<tr>
<td>FEV₁ (ml⁻¹)*</td>
<td>932 (413)</td>
<td>803 (216)</td>
<td>n.s.</td>
</tr>
<tr>
<td>FEV₁ (% pred.)*</td>
<td>61.7 (23.1)</td>
<td>56.1 (16.0)</td>
<td>n.s.</td>
</tr>
<tr>
<td>PAO₂ (mmHg)*</td>
<td>67.6 (9.7)</td>
<td>62.2 (15.6)</td>
<td>n.s.</td>
</tr>
<tr>
<td>PACO₂ (mmHg)*</td>
<td>43.4 (9.0)</td>
<td>43.5 (6.9)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Δ FVC (ml⁻¹)†</td>
<td>-117.1 (314.4)</td>
<td>-229.2 (475.7)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Δ FEV₁ (ml⁻¹)†</td>
<td>-104.3 (81.6)</td>
<td>-63.1 (202.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>ΔPAO₂ (mmHg)†</td>
<td>1.4 (4.4)</td>
<td>-1.1 (9.5)</td>
<td>n.s.</td>
</tr>
<tr>
<td>ΔPACO₂ (mmHg)†</td>
<td>1.1 (32)</td>
<td>0.9 (2.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Emergence antibiotic-resistant bacteria</td>
<td>1/7</td>
<td>4/8</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*Values are means ± SEM.
†Change over time.
ns., not significant.
We studied a group of difficult-to-control non-CF patients with severe lung disease secondary to bronchiectasis and CBIPA. Although this was an uncontrolled trial, our results suggest that these patients could benefit from long-term inhaled antibiotic therapy. However, the time scale and frequency of treatment as well as the type, dose and amount of antibiotics cannot be definitively recommended at this time.

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References