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Nebulized Tobramycin in patients with chronic respiratory infections during clinical evolution of Wegener's Granulomatosis

C. TERZANO, A.E. TAURINO*, V. PEONA*

Dipartimento di Scienze Cardiovascolari e Respiratorie, "La Sapienza" University - Rome (Italy)
**Istituto Malattie dell'Apparato Respiratorio, Università of Pavia (Italy)*

Abstract. – **Aminoglycosides are effective against *Pseudomonas aeruginosa* but with intravenous administration there are only very low concentrations achieved in sputum; therefore in order to obtain therapeutic levels in patients with endobronchial infections should be administered high doses with increased likelihood to produce both nephrotoxic and ototoxic effects.**

Direct aerosol delivery of aminoglycosides to the lower respiratory tract has the advantage to achieve high antibiotic sputum concentrations in the infected area with reduced risk of systemic toxic reactions because of minimal absorption into the circulation.

Nowadays, except for patients suffering from cystic fibrosis and bronchiectasis, the administration of antibiotics through inhalers is not very much in use.

The aim of this study was to administer nebulized tobramycin in chronic respiratory infections developed during the evolution of Wegener's Granulomatosis in order to obtain data concerning the safety and efficacy of inhaled aminoglycosides.

The results obtained underlined an improvement in FEV_1, FEF_{75} and PaO_2.

The aerosolized tobramycin administered in 300 mg doses three times per day for four weeks, showed itself to be effective and safe, not causing any undesirable clinical or microbiological side-effects.

Moreover, a long term treatment has been shown to control the *Pseudomonas aeruginosa* infection on the bronchial system in Wegener's granulomatosis and reduce the frequency of exacerbations in chronic patients.

Key Words:

Aerosol, Tobramycin, Wegener' Granulomatosis, Pseudomonas aeruginosa.

Introduction

Epidemiological data suggest that chronic endobronchial infections caused by *Pseudomonas aeruginosa* (PA) are significantly associated with a more rapid decline in pulmonary function and increased hospitalisation.

This infection is associated to a faster development of obstructive lung disease since the bacteria adapt to the environment of the airways with the result that it is much more difficult to fight with a treatment of antibiotics which might make the respiratory system sterile once again.

Aminoglycosides are effective antibiotics for the *Pseudomonas aeruginosa* infection treatment but they only penetrate a little into the endobronchial secretions making it necessary to administrate large doses parenterally and exposing the patients to complications connected to ototoxicity and kidney toxicity, which are characteristic of this class of antibiotics.

The aerosol administration of aminoglycosides for the treatment of PA chronic infections has been studied mostly on groups of patients suffering from cystic fibrosis[1,2].

Although, until now, the duration of therapy, how often the drugs are administered and the parameters which can be considered as a reference in ascertaining the validity of the intervention have been not defined, the majority of the studies underline an improved evolution of some aspects of the chronic infection after a period of aerosol therapy[3-5].

Thus the aerosol delivery of antibiotics might be an interesting proposal for the

treatment of bronchopulmonary infections since, theoretically, it should allow for a better local concentration of the drug followed by a minor presence of side-effects compared to the systemic administration[2,6,7].

Unfortunately, the delivery of tobramycin through inhalation containing excipients such as phenol and metabisolphite, even when well tolerated, can lead to bronchial inflammatory disease, with consequent airflow obstruction and/or cough, mostly in people suffering from bronchial hyperreactivity.

Presence of a relevant reduction of FEV_1 have been observed after aerosol delivery of antibiotics, and in particular in people suffering from atopic asthma. In these cases not even the preventive administration of β2-agonists and cromons offered protection from airflow obstruction[8].

Moreover some authors have observed that cough and airflow obstruction are more marked when using nebulizers which deliver particles with an aerodynamic diameter bigger than 2 μm, concluding that these side-effects are the result of an increase in the size of particles with a consequent drugs regional deposition at the level of the large airways[9].

Nevertheless, those particles with an aerodynamic diameter lower than 2 μm, mostly deposited in the small airways[10], may lead to a larger systemic absorption of the drug inhaled and, consequently, to a larger presence of undesirable side-effects which, in the case of tobramycin are, besides cough and airflow obstruction, tinnitus, hemoptysis, and increased creatinine levels.

At the present time, except for those patients suffering from cystic fibrosis and bronchiectasis the aerosol delivery of antibiotic is not much used and the possibility of delivering tobramycin with β2-agonists (salbutamol) has been proposed because of the chemical compatibility of the two drugs[11,12].

Furthermore, not all the studies have shown the real activity of the aerosolized antibiotic therapy. In particular aerosol administered tobramycin has showed itself capable of efficiently treating the infections due to *Pseudomonas aeruginosa* in 63% of the patients, whereas only 25% of the patients who have undergone intravenous therapy have been cured. No relevant benefits have been reached at adding aerosolized tobramycin to the systemic therapy in patients suffering from cystic fibrosis[13].

The variability of the results may partly depend on the characteristics of the patients with regard to sex, age, breathing patterns, localization and gravity of the pathology, and the way the drug is administered through inhalation, particularly the type of appliance used and size of particles nebulized.

In fact in few studies granulometric measurement of aerosolized antibiotics has been done and kinetics of delivered drug evaluated.

In particular size measurement of particles nebulized is still a very complex and much discussed problem.

Alternative instruments to the cascade impactor have been proposed. Such instruments are those which resort to light scattering or to time of flight aerosol beam spectrometers.

In this study a time of flight aerosol beam spectrometer (API Aerosizer – Amherst – MA-USA) was preferred because of its technical characteristics, guarantees more accuracy and can be repeated compared to other instruments which resort to the light scattering technique.

Moreover, the size of the particle given off by three different pneumatic jet nebulizers has been measured to find the one offering the largest peripheral deposit of the drug.

Considering what is written in studies about the safety and efficacy of the administration of aerosolized aminoglycosides[2,14] this therapy has been applied to chronic respiratory infections during clinical evolution of Wegener's Granulomatosis.

In this vasculity, infections in large and lower airways are present in the disease remission phases and, like in the cystic fibrosis, they are supported by PA and/or *Staphylococcus aureus* which is one of the main causes leading to exacerbations.

The selection of female patients has contributed to avoid one of the most important variables of pulmonary deposition of the inhaled drug regarding individual anthropometric data.

Patients and Methods

Patients

7 patients have been taken into consideration (Table I). Between 1997 and 1999 they asked to be put under observation because of the outbreak of some symptoms caused by an acute pulmonary disorder. All the patients who had been diagnosed as having Wegener's granulomatosis were women, had a stable infection due to PA for an average of 20 months and had taken Ciprofloxacin at least once in the last year. Moreover, two patients are both infected by *Staphylococcus aureus*, which had been isolated at each visit during periodical check ups. Consent was given by all the patients to the use of their own clinical data before the study.

After clinical evaluation (functional, respiratory and bacteriological) of each patient, a home therapy comprising salbutamol (3 mg) and aerosolized tobramycin (300 mg) three times per day for four weeks was prescribed.

The antibiotic with the addition of salbutamol to avoid airflow obstruction and cough and to increment the mucociliary clearance was nebulized using a jet nebuliser (Nebula Nuovo – MEFAR – Bovezzo – (Brescia) – Italy).

Aerosol therapy after postural draining was advised, and this had already been carried out on some patients as routine.

Each patient was taught to use the aerosol therapy with a nebulizer according to that stated by the Società Italiana per gli Aerosol in Medicina[15].

Patients with both PA and SA colonization were treated with tobramycin and also with rifampicin (600 mg per day).

Table I. Clinical data of the patients at the beginning of the study.

N. People	7
Age	58 (± 29,5)
PA/S. Aureus infection	7/2
Infection due to PA (months)	20,1 (± 10,25)
FEV_1 (percentage)	-16,6% (± 12,75)
PaO_2 (mmHg)	70,62 (± 8,82)

In order to evaluate variations of the respiratory functions, FEV_1, FEF_{75} and arterial oxygen saturation have been considered both at the end of the treatment and two weeks later (follow up).

In order to evaluate the therapy's long term effects, the number of pneumologic visits requested by each patient in the six months after the suspension of the therapy was taken as a point of reference, comparing it with the corresponding six months of the previous year.

Particle sizing experiments

In order to determine the size of the particles (aerosol characterization) in the distribution of 300 mg of tobramycin + 3 mg of salbutamol produced by each of the three tested appliances for the duration of two seconds, an Aerosizer Mach 2 (Amherst Process Instruments Inc, Amhesrt-MA) was used the function of which is based on the technique called Time of Flight Aerosol Beam Spectrometry (TOFABS).

The granulometric study was carried out at an ambient temperature of 27° C and a relative humidity of 53%.

Sputum tobramycin levels

All patients swallowed a 40 ml aliquot of water after gargling, immediately after nebulization to remove tobramycin deposited in the oropharynx. The sputum samples were ultrasonicated to liquid, diluted in TDX buffer and fluoro-immunoassayed on the Abbott TDX analyzer.

Statistical analysis

Pulmonary functions tests and PaO_2 were compared using Student's t-test. An error probability of 5% was regarded as significant.

Results

Patients

All the patients inhaled tobramycin + salbutamol for a period of 28 days after which they underwent a clinical revaluation comprising haematochimic checks, chest radiography, spirometric test, hemogasanalysis and sputum cultural check.

Table II. Evaluation of the functional values at the end of treatment (period B) compared with the values previously recorded (period A) and two weeks after therapy (period C).

	Period A	Period B	Period C	P
FEV_1 (%)	-16.66 (± 12.75)	- 10.9 (± 14.1)	- 12.2 (± 6.52)	N.S.
FEF_{75} (%)	-70.3 (± 9.35)	- 67.5 (± 10.56)	- 68.2 (± 11.2)	N.S.
PaO_2 (mmHg)	70.62 (± 8,82)	78.01 (± 4.57)	76.8 (± 4.45)	N.S.

N.S.: non significant.

At the end of the therapy the FEV_1 and FEF_{75} values indicated an improvement in the ventilatory function (Table II). This improvement was on an average of 6.5% for FEV_1 and 9.4% for FEF_{75}, whereas it was 4.9% and 6.6% for FEV_1 and FEF_{75} respectively if the values recorded two weeks later are compared with those of the period before the treatment.

The average value of FEV_1 and FEF_{75} was recorded as being 5.92% and 8.98% among the values after therapy was suspended, if patients who were not affected by *S. aureus* were considered. In fact in the treatment of the two patients infected by both bacteria, the use of rifampicin might have influenced the improvement of the ventilatory function.

Taking into consideration the functional values recorded for each patient (Table III) it is possible to notice that in the fourth case, corresponding to the oldest patient, the functional values, recorded after two weeks, are reduced compared to those recorded before the beginning of the therapy.

Table III. Functional values recorded at the end of the inhalatory treatment with tobramycin (period B), two weeks after the end of the therapy (period C) and before the therapy (period A)..

Cases	Period A	Period B	Period C
I Case	FEV_1 – 16.7%	FEV_1 – 9.7%	FEV_1 – 11%
	FEF_{75} – 76.6%	FEF_{75} –75%	FEF_{75} – 75%
II Case*	FEV_1 – 10.2%	FEV_1 – 2.7%	FEV_1 – 1.6%
	FEF_{75} – 75.3%	FEF_{75} – 73%	FEF_{75} – 71.4%
III Case	FEV_1 – 4.9%	FEV_1 + 0.5%	FEV_1 – 0.5%
	FEF_{75} – 76.1%	FEF_{75} – 74.3%	FEF_{75} – 76.1.%
IV Case	FEV_1 – 4.8%	FEV_1 + 2.4%	FEV_1 – 6.02%
	FEF_{75} – 70%	FEF_{75} – 67%	FEF_{75} – 71%
V Case	FEV_1 – 54.8%	FEV_1 – 52.1%	FEV_1 – 53.2%
	FEF_{75} – 79%	FEF_{75} – 77.3%	FEF_{75} – 78.1%
VI Case	FEV_1 – 22%	FEV_1 – 19%	FEV_1 – 19.6%
	FEF_{75} – 73.8%	FEF_{75} – 70.8%	FEF_{75} – 72.8%
VII Case*	FEV_1 – 3%	FEV_1 + 4.3%	FEV_1 + 6.5%
	FEF_{75} – 41.6%	FEF_{75} – 35%	FEF_{75} – 33.3%

*Patients with infection due to S. aureus plus PA.

With regards to the activity of aerosol therapy in the prevention of the acute infection recorded, compared to pneumological check ups during the six months after the aerosol therapy with tests during the corresponding previous year, the resulting data indicate that in the six months after the therapy only four patients did not have to undergo a medical revaluation, and among these there are those who had been cured with rifampicin.

The pneumonologic check ups requested were, on average, 1 in the months following therapy, whereas they had been 2.4 in the corresponding months the year before.

At any rate, considering patients with only the infection due to PA, the average number of check ups in the months following therapy, were fewer than those with whom the comparison must be made (1.4 whereas for the reference period the average is 3).

Sputum tobramycin concentrations

The peak sputum tobramycin level exceeds 100 mg 1^{-1} in all the patients.

Discussion

The activity of aerosolised tobramycin is based on the idea that it can reach high concentrations in the infected area giving few or no side effects due to systemic absorption.

Nonetheless, the aerosolized administration of drugs and their deposition in the lower airways is influenced by many factors, among which are type of nebulizer used, physical-chemical features of the drugs and their concentration in the aerosol, size of the particles, pressure in the compressor and individual ventilatory function.

Moreover, the pulmonary disease, for instance in hypo or non-ventilated areas, may determine the reduction or non-deposit of the drug.

Thus the dose of the inhaled drug deposited in the infected area is extremely variable.

In our study tobramycin was administrated through a jet nebulizer, Nebula Nuovo.

This device was chosen to deliver the drug to the site of infection in the airways rather than the alveoli.

In fact, reducing the deposition of the drug on the alveolar surface, the systemic absorption tends to be limited and thus the undesirable side-effects[10].

The aerosolized administration of aminoglycosides for the treatment of chronic infections due to PA has been mostly studied on groups of patients suffering from cystic fibrosis.

Although the duration of the therapy, the frequency of administration and the parameters which can be considered as being a point of reference to ascertain the validity of the intervention have not been defined until now, almost all studies state an improvement in the evolution of some aspects of chronic infections after aerosol therapy[5,16].

In this study with aerosolized tobramycin administered for 28 days patients suffering from Wegener's Granulomatosis were found to have an improvement of FEV_1, FEF_{75} and PaO_2 as the values after therapy indicate; these variations have a limited value considering the fact that the antibiotic was routinely aerosolized using a bronchodilator. It is probably more interesting to note that the values of the functional data did not show signs of worsening two weeks after the administration of tobramycin had been suspended.

It is important to stress that in the case of the oldest patient the functional values noted were reduced compared to those recorded before therapy, whereas in the two patients infected by *S. aureus* as well, the improvement might have been influenced by taking rifampicin at the same time. In fact these two patients were the ones who needed fewer medical check ups than the others.

The other two patients who had no symptoms for six months after therapy, at a successive check up, said that after the initial administration of aerosolized antibiotics, following an increase in expectoration with variations in color, they had independently prescribed themselves aerosolized antibiotics on at least two other occasions. In these patients too, there were neither alterations of kidney functions nor any other

side effects, at the moment of the routine visits.

The administration of aerosolized tobramycin in the sample taken into consideration can therefore be considered to be safe, as it did not produce any undesirable clinical or microbiological side effects.

In particular in none of the cases the emergence of PA resistant to tobramycin was noted, not even in those patients who had taken antiobiotics on their own prescription.

As this is a preparation used parenterally there may be the risk of airways irritation.

The contemporary administration of salbutamol not only avoided reflex phenomena, such as coughs and bronchospasms, but it also helped to gather the expectoration to determine the concentration of tobramycin.

This study, directed to show the efficacy and clinical advantages of aerosolized tobramycin therapy in patients suffering from chronic infections by PA, with particular reference to Wegener's Granulomatosis, offers results which are not easy to understand, like many other studies based on patients suffering from cystic fibrosis or other respiratory pathologies[17].

The important result is a slowed frequency of acute infections in the six months after aerosol therapy with a reduction in the number of check ups.

On the other hand, without considering the low prevalence of the disease, the particular pathology we took into consideration advises one not to compare evaluations with placebo as this could be unfavourable for the patient.

In our study the peak sputum tobramycin level exceeds 100 mg 1^{-1} in all the patients, whereas the jet nebulizer Nebula Nuovo was chosen because, among those we tested, it was the one which delivered the smallest percentage of particles with an aerodynamic diameter < 2 µm, these being the ones that prevalently reach the pulmonary tract, where the greater part of the systemic absorption of the inhaled drug takes place.

The drug reaching pulmonary vessels through the alveolar structures have to cross a barrier constituted by surfactant, epithelium and interstitium. In particular they can pass through the cells, between two cells, or in spaces left by dead cells. In the latter case, together with the opening of the tight junctions, it is possible for many pulmonary pathologies to be observed; for instance as in BPCO and, in our case, Wegener's granulomatosis.

In these cases the lungs are more permeable to drugs compared to those of healthy people. It is therefore necessary to reduce drug deposit at the small airways and alveoli level as far as possible[18].

In an our previous study it was shown that differences in the performance of nebulizers influence therapeutic effects and tobramycin deposit in the lower airways[19]. As a matter of fact, this having its basis on the application of mathematical models, might establish that the device we selected allows the largest concentration of medicine in the infected area.

Besides, at present there are no studies supporting the routine use of antibiotics by inhalation as a replacement for, or as an adjunct to, parenteral antibiotics for the treatment of a pulmonary exacerbation.

As stressed by Campbell et al.[20] there may be individual situations when an aerosolized antibiotic may be used by itself or together

Table IV. Aerosol characterization of the three nebulizers (± SD).

Nebulizer	*MMAD*	*GSD*	*% 5-2*	*% < 2*
Nebula Nuovo*	3.7 (0.04)	2.3	71.21 (0.72)	9 57 (0.62)
Pari IS2**	3.1 (0.05)	1.6	80.13 (0.44)	15.79 (0.10)
Artsana***	3.0 (0.04)	2.3	82.87 (0.46)	14.69 (0.38)

*Nebula Nuovo compressor plus MB3 nebulizer; **Pari IS2 compressor plus LC Plus nebulizer; ***Artsana compressor plus Sidestream nebulizer.
MMAD = Mass Median Aerodynamic Diameter (µm); GSD = Standard Geometric Deviation; % 5-2: particles percentage between 2 and 5 µm; % < 2 : particles percentage smaller than 2 µm.

with parenteral antibiotics and/or an oral fluoroquinolone for the treatment of a pulmonary exacerbation, and in two of our patients it was necessary to add another antibiotic because of a further bacterial infection by *S. aureus*. This fact stresses the importance of what has been completed in the present study: a continuous monitoring of the efficacy of initial therapy with repeated clinical check ups and an immediate correction of the therapy in the case of complications.

Briefly, our study demonstrates not only that the long term treatment with tobramycin (300 mg three times a day for four weeks) can control or at least reduce *P. aeuruginosa* infection in the bronchial system in Wagener's Granulomatosis patients, but also that (1) the configuration of the nebulizer can potentially affect both the amount of aerosolized tobramycin inhaled as well as the particle size and therefore needs to be specified precisely in the protocols; (2) moreover, since other factors can influence the dose of drug deposited in the lower airways, it is necessary, after having selected the device to be used, to standard the inhalation of the delivered drug through a nebulizer and its maintenance. The guidelines in Aerosolterapia by SIAM we used have been very useful both for the medical and technical staff and patients[15]; (3) the clinical and functional check up of the patients is the basis for all the therapies, allowing through repeated monitoring, to verify the efficacy of the prescribed therapy and, eventually, to intervene correcting or modifying the previous therapeutic model.

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