Pulmonary deposition of inhaled tobramycin prior to and after respiratory therapy and use of inhaled albuterol in cystic fibrosis patients colonized with *Pseudomonas aeruginosa**

Deposição pulmonar de tobramicina inalatória antes e após fisioterapia respiratória e uso de salbutamol inalatório em pacientes com fibrose cística colonizados por *Pseudomonas aeruginosa*

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Abstract

Objective: To evaluate whether respiratory therapy followed by the use of inhaled albuterol modifies the pulmonary deposition of inhaled tobramycin in patients with cystic fibrosis (CF) and whether pulmonary deposition correlates with disease severity or genotype. **Methods:** A prospective study was carried out including patients with CF older than 6 years of age and colonized with *Pseudomonas aeruginosa*. Exclusion criteria were pulmonary exacerbation, changes in therapy between the study phases and FEV_1 < 25%. All patients were submitted to pulmonary scintigraphy by means of a scintillation camera equipped with a low-energy all-purpose collimator in order to evaluate drug penetration following the administration of inhaled ^{99m}Tc-tobramycin, as well as to pulmonary perfusion with ^{99m}Tc-macroaggregated albumin (phase 1). One month later, the same procedure was performed following respiratory therapy and administration of inhaled albuterol (phase 2). **Results:** We included 24 patients (12 males) aged 5-27 years (mean ± SD: 12.85 ± 6.64 years). The Shwachman score (SS) was excellent/good in 8 patients, moderate/fair in 16 and poor in 0. Genotyping revealed that 7 patients were ΔF508 homozygotes, 13 were ΔF508 heterozygotes; and 4 presented other mutations. In all patients, lung deposition of tobramycin decreased in phase 2, especially in those with moderate/fair SS ($p = 0.017$) and in heterozygotes ($p = 0.043$). **Conclusions:** The use of a respiratory therapy technique and the administration of inhaled albuterol immediately prior to the use of inhaled tobramycin decreased the pulmonary deposition of the latter in CF patients, and this reduction correlates with disease severity and genotype.

Keywords: Cystic fibrosis; Tobramycin; Respiratory therapy; Albuterol; Radionuclide imaging.

Resumo

Objetivo: Avaliar se a fisioterapia respiratória seguida do uso de salbutamol inalatório modifica a deposição pulmonar de tobramicina inalatória em pacientes com fibrose cística (FC) e se a deposição pulmonar apresenta correlação com a gravidade da doença ou com o genótipo. **Métodos:** Um estudo prospectivo foi realizado com pacientes com FC maiores de 6 anos e colonizados por *Pseudomonas aeruginosa*. Os critérios de exclusão foram exacerbação pulmonar, mudança terapêutica entre as fases do estudo e VEF_1 < 25%. Todos os pacientes foram submetidos à cintilografia pulmonar com câmara de cintilação com um colimador *low energy all purpose* para avaliar a penetração da droga após a inalação de tobramicina marcada com tecnécio (^{99m}Tc-tobramicina), e à perfusão pulmonar com ^{99m}Tc-macroagregados de albumina (fase 1). Após um mês, foi realizado o mesmo procedimento precedido de fisioterapia respiratória e administração de salbutamol inalatório (fase 2). **Resultados:** Foram incluídos 24 pacientes (12 masculinos) com idade variando de 5 a 27 anos (média ± dp: 12,85 ± 6,64 anos). O escore de Shwachman (ES) foi excelente/bom em 8 pacientes, moderado/regular em 8 e grave em 0. A genotipagem revelou que 7 pacientes eram ΔF508 homozigotos, 13 eram ΔF508 heterozigotos, e 4 apresentavam outras mutações. A deposição pulmonar da tobramicina foi menor na fase 2 em todos os pacientes, sendo menor nos pacientes

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com ES moderado/regular (p = 0,017) e também nos heterozigotos (p = 0,043). **Conclusões:** O uso de uma técnica de fisioterapia respiratória e a administração de salbutamol inalatório imediatamente antes do uso de tobramicina inalada diminuem a deposição pulmonar desta última em pacientes com FC, e esta redução tem correlação com a gravidade da doença e genótipo.

Descritores: Fibrose cística; Tobramicina; Terapia respiratória; Albuterol; Cintilografia.

Introduction

The improvement in treatment and quality of life of patients with cystic fibrosis (CF) is principally due to the effectiveness of the antibiotics used to prevent and control pulmonary infection, the principal cause of CF-related morbidity and mortality.[1]

In industrialized countries, the systematic use of antibiotics has resulted in an increase in the survival of these patients, from 14 years in 1969 to over 30 years in 2001.[2] However, 80% of patients with CF will be colonized with *Pseudomonas aeruginosa*, and 90% will evolve to terminal chronic progressive lung disease.[3] The age of the onset of the chronic infection with *P. aeruginosa* is a predictor of the age of death.[4]

It is believed that the increase in the prevalence and the early appearance of *P. aeruginosa* colonization is due to the continuous use of the antibiotic therapy against the *Staphylococcus aureus*. Various studies discuss this hypothesis, with confirming findings in various research centers in Canada,[5] the USA, [6] Germany[7] and the United Kingdom.[8]

In the 1970s and 1980s, the emphasis in the treatment was intravenous antibiotic therapy against infection with *P. aeruginosa*, and this treatment improved survival.[1]

However, intravenous administration of antibiotics is limited by a series of factors: many antibiotics have poor penetration in the sputum, and require high doses to produce effective concentrations, in addition to presenting higher risks of ototoxicity, vestibulotoxicity and nephrotoxicity.

These complications usually lead to hospitalization, which can interrupt the social and educational life of the child, resulting in an increase in the cost of the disease and in the risk of exposure to nosocomial infection.[9]

Despite the clinical and pulmonary function improvement, the intravenous antibiotic therapy has a transitory effect, with return of the sputum bacterial density to pre-treatment levels in 2 to 6 weeks after the end of the treatment.[10] Therefore, the chronic administration of oral antibiotic therapy has been proposed in many centers as a means of preventing bacterial colonization.

Subsequently, the interest in the administration of antibiotics through inhalation, due to the advantage of drug deposition directly at the site of infection as well as the reduction of the risk of systemic toxicity.[11]

Various studies on inhaled antibiotics (IAs) have produced encouraging results, such as pulmonary function improvement,[11-15] or a slowing of pulmonary function deterioration,[12,16,17] and a reduction in the number of hospitalizations.[11,15,17]

The most widely used IAs are the aminoglycosides, since they present a prolonged effect, lower systemic toxicity, a pleasant taste and low bacterial resistance when used intermittently.[18]

The variability in the pulmonary deposition of IAs has been studied, and various factors, in isolation or in combination, have been presented as a barrier to the passage and distribution of the aerosols in the airways of the patients with CF. Among such factors, the following have been cited: greater viscosity of the mucus,[16] obstruction of the air flow by a secretion plug, poor mucociliary clearance, size of the inhaled particles and type of inhaler used.[20]

A few studies, in which the bronchopulmonary deposition of radioaerosols was quantified, have presented similar results. One of those studies revealed that only approximately 7% of the inhaled tobramycin reaches the lungs, and that only 16% of this is deposited peripherally.[21] In another study, it was concluded that 10% of the inhaled tobramycin was deposited in the lungs, and that 90% was either trapped in the oropharynx, swallowed or exhaled to the atmosphere.[22]

Another group of authors proved the occurrence of IA-induced bronchospasm, demonstrating alterations in the pulmonary function test results and constriction of the smooth bronchial muscles after the use of inhaled colistin.[22]

It has been suggested that the use of IAs should be preceded of respiratory therapy, as

well as by the use of bronchodilators, mucolytic agents or human recombinant DNase in an attempt to remove obstructions from the bronchial tree, thereby decreasing induced bronchospasm and increasing lung penetration of the antibiotic.[24]

The objective of this study was to evaluate the pulmonary deposition of inhaled tobramycin in CF patients colonized with *P. aeruginosa*. To that end, we used lung scintigraphy, comparing the penetration of this radioactive drug prior to and after the use of bronchial clearance measures, with the use of respiratory therapy and inhaled albuterol, as well as reporting these data with a severity and mutation score.

Methods

A clinical prospective longitudinal intervention study was carried out. Patients were selected from among those treated between June and November of 2005 at the Cystic Fibrosis Outpatient Clinic of the *Hospital das Clínicas da Universidade Estadual de Campinas* (HC-Unicamp, State University at Campinas *Hospital das Clínicas*), located in Campinas, Brazil. The following inclusion criteria were applied: being over 6 years of age; having been diagnosed with CF; having received diagnostic confirmation based on a suggestive clinical history, at least two sweat tests, using the pilocarpine iontophoresis method, with altered results or identification of two mutations in the gene that encodes the cystic fibrosis transmembrane regulator (CFTR) protein; and being chronically colonized with *P. aeruginosa*, confirmed by three positive sputum cultures or oropharyngeal swab, during a six-month follow-up period.

Patients with signs of acute respiratory failure (pulmonary exacerbation) at the time of the tests were excluded, as were those requiring a change in therapy between the phases of the study or presenting an FEV_1 < 25% of predicted.

Age and gender were recorded at the onset of the examinations.

The Shwachman score (SS) evaluates the clinical severity of the patients with CF using clinical criteria of nutrition, general activity, physical examination and radiographic findings. The score was evaluated by three physicians according to the criteria recommended by the original author,[25] and a mean of the values found was calculated. Patients with mean scores > 70 were classified as good/excellent, whereas those with mean scores from 41 to 70 were classified as moderate/fair, and those with mean scores < 40 were classified as severe.

The mutation of the gene encoding the CFTR was studied in each patient at diagnosis by the hospital genetics team.

Study design

Phase 1: Patients were submitted to pulmonary scintigraphy with technetium (^{99m}Tc)-labeled tobramycin inhalation and to pulmonary perfusion with ^{99m}Tc-labeled macroaggregated albumin (^{99m}Tc-MAA), in order to evaluate the isolated penetration of the drug into the bronchial tree.

Phase 2: After a month, the patients were submitted to bronchial clearance measures with respiratory therapy using the Flutter VRPI® device (Scandipharm Inc., Birmingham, AL, USA)[26,27] and inhalation with inhaled albuterol (200 μg), using a spacer in patients aged 6 years or a mouthpiece in patients older than 6 years of age. Patients were then again submitted to the inhalation of the radioactive drug, to pulmonary scintigraphy and to pulmonary perfusion, using the same acquisition parameters.

Tobramycin labeling followed methods described for other aminoglycosides.[21] A solution was prepared by dissolving 10 mg of stannous chloride in 10 mL of hydrochloric acid (adding 0.5 μL of fuming hydrochloric acid to 9.5 mL of distilled water). To 50 mL of this solution, 3 mL (120 mg) of tobramycin were

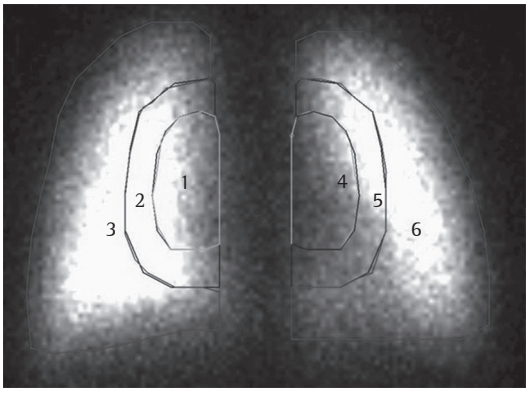

Figure 1 - Regions of interest of the pulmonary uptake of inhaled ^{99m}Tc-tobramycin: 1: right central; 2: right middle; 3: right peripheral; 4: left central; 5: left middle; and 6: left peripheral.

added. The mixture was submitted to a flow of nitrogen for 10 min in order to remove free oxygen from the solution. Using a pH indicator paper, pH, which should remain at approximately 6.0, was measured. For the preparation of the inhaled radioactive drug, the pH was corrected with a sodium hydroxide solution until pH 8-9 was reached. Subsequently, the ^{99m}Tc pertecnetate (30 mCi in 0.5 mL of 0.9%-saline solution), and the mixture was filtered using a 0.22-μm membrane filter (Millipore Corporate Headquarters, Billerica, MA, USA). Quality control of the filtrate was conducted, and that was transferred to the inhalation flask with the quantity of material necessary for one patient.

The labeling yield of the ^{99m}Tc-tobramycin was approximately 87%.

Inhalation of the ^{99m}Tc-tobramycin was carried out according to the security measures for radioactive material. Therefore, a disposable closed-circuit (UltraVent™; Mallinckrodt Medical Inc., St. Louis, MO, USA) with 1 mL of 99mTc-tobramycin was used.

The patient was prepared for inhalation, remaining seated in a chair, hair covered by a disposable cap and the body covered with a white cotton sheet.

The mouthpiece was properly adjusted in the mouth, and the nose was closed with a disposable nasal clip The patient was asked to breathe slowly and deeply through the mouth for 10 min. After this procedure and before the removal of the disposable material, the patients gargled with water to eliminate residues of radioactive material present in the mouth.

After inhalation, the patient was placed in the examination room in the horizontal supine position, and static images of pulmonary scintigraphy were obtained in a scintillation camera equipped with a low-energy all-purpose colli-

Table 1 - Comparison of the values of pulmonary deposition of inhaled ^{99m}Tc-tobramycin in all lung segments in phases 1 and 2 (n = 24).

Lung segment	Study phase	Mean[a]	SD[a]	Mean error[a]
1	1	24,799.76	16,989.48	3,467.96
1	2	20,191.63	12,653.27	2,582.84
2	1	42,552.54	13,846.37	2,826.38
2	2	36,087.29	11,046.60	2,254.86
3	1	75,016.04	23,916.03	4,881.84
3	2	69,258.33	21,547.59	4,398.38
4	1	26,975.96	18,421.29	3,760.23
4	2	22,081.21	13,818.02	2,820.59
5	1	42,149.96	10,786.91	2,201.87
5	2	37,165.67	8,501.17	1,735.29
6	1	74,279.67	22,570.54	4,607.19
6	2	68,824.04	18,753.72	3,828.09
7	1	17,690.83	6,084.02	1,241.90
7	2	15,997.13	4,868.52	993.78
8	1	35,791.71	12,947.40	2,642.88
8	2	32,739.96	9,825.77	2,005.68
9	1	70,345.96	26,122.23	5,332.18
9	2	60,922.50	20,545.37	4,193.81
10	1	21,332.79	8,759.26	1,787.98
10	2	19,474.21	5,957.48	1,216.07
11	1	40,219.71	15,000.59	3,061.98
11	2	35,882.00	10,226.98	2,087.57
12	1	74,794.21	25,612.43	5,228.11
12	2	67,807.67	19,924.53	4,067.08

1: region of interest (RI) 1, right anterior lung (internal region); 2: RI 2, right anterior lung (middle region); 3: RI 3, right anterior lung (posterior region); 4: RI 1, right posterior lung (internal region); 5: RI 2, right posterior lung (middle region); 6: RI 3, right posterior lung (posterior region); 7: RI 4, left anterior lung (internal region); 8: RI 5, left anterior lung (middle region); 9: RI 6, left anterior lung (posterior region); 10: RI 4, left posterior lung (internal region); 11: RI 5, left posterior lung (middle region); and 12: RI 6, left posterior lung (posterior region). [a]Values in kilocounts.

mator with 500 kilocounts. Subsequently, static images of perfusion with injection of ^{99m}Tc-MAA were obtained.

The Flutter® device maneuvers were carried out with all patients in two stages. In the first stage, 10 respirations were performed with the objective of releasing and mobilizing the mucus. Initially, patients assumed an erect and relaxed position, inhaled normally and slowly, without filling their lungs completely, held their breath for 2-3 s, placed the Flutter® device in their mouth, adjusted the inclination and, with rigid cheeks, exhaled with reasonable speed, although not with forced speed and without emptying their lungs completely, attempting to avoid coughing. In the second stage, the procedure was performed twice, with the objective of eliminating the mucus. Patients inhaled slowly, filling their lungs completely, held their breath for 2-3 s, placed the Flutter® device in their mouth, adjusted the inclination and, with rigid cheeks, exhaled vigorously through the Flutter® device, emptying their lungs as completely as possible. Finally, cough was initiated spontaneously or through huffing. The procedure was performed a total of 10 times, supervised by the same previously trained physical therapist.

The administration of inhaled albuterol was performed immediately after the end of the respiratory technique, and the pulmonary scintigraphy was performed 15 to 30 min afterwards.

The images acquired in phases 1 and 2 were quantified and classified according to the region of interest defined in the internal, middle and peripheral portions of both lungs (Figure 1).

Statistical analysis

The paired t-test was used in the same patients prior to and after the performance of the respiratory therapy and the administration of inhaled albuterol in order to evaluate the lung penetration of the ^{99m}Tc-tobramycin.

The t-test for paired samples was used to compare the means of two variables (simple group). For each case, the difference between the values of the two variables was calculated, as whether the mean was different from 0 was tested. Mean, sample size, SD and standard error of the mean were calculated for each variable.

Correlation, t-test, mean difference and 95% CI, as well as the SD and standard error of the mean difference, were used for each pair of variables compared (prior to and after respiratory therapy) For data processing, we used the software Statistical Package for the Social Sciences, version 7.5.1 (SPSS Inc., Chicago, IL, USA).

The study was approved by the Ethics Committee of the HC-Unicamp School of

Table 2 - Comparison of the values of pulmonary deposition of inhaled ^{99m}Tc-tobramycin in all lung segments in phases 1 and 2, using the paired t-test with 95% CI.

Lung segment	Mean[a]	SD[a]	Mean error	95% CI		p
				Minimum[a]	Maximum[a]	
1	4,608.13	6,916.35	1,411.79	1,687.61	7,528.64	0.003
2	6,465.25	9,032.72	1,843.80	2,651.07	10,279.43	0.002
3	5,757.75	18,424.67	3,760.92	−2,022.35	13,537.77	0.139
4	4,894.75	7,381.34	1,506.70	1,777.88	8,011.62	0.004
5	4,984.29	8,210.77	1,676.02	1,517.19	8,451.40	0.007
6	5,455.67	16,892.25	3,448.12	−1,677.35	12,588.60	0.127
7	1,693.71	4,094.79	835.85	−35.37	3,422.79	0.054
8	3,051.75	7,907.56	1,614.12	−287.32	6,390.82	0.071
9	9,423.46	17,959.15	3,665.90	1,839.97	17,006.94	0.017
10	1,858.58	6,603.22	1,347.88	−929.71	4,646.88	0.181
11	4,337.71	9,967.94	2,034.70	128.62	8,546.80	0.044
12	6,986.54	15,060.82	3,074.28	626.91	13,346.17	0.033

1: region of interest (RI) 1, right anterior lung (internal region); 2: RI 2, right anterior lung (middle region); 3: RI 3, right anterior lung (posterior region); 4: RI 1, right posterior lung (internal region); 5: RI 2, right posterior lung (middle region); 6: RI 3, right posterior lung (posterior region); 7: RI 4, left anterior lung (internal region); 8: RI 5, left anterior lung (middle region); 9: RI 6, left anterior lung (posterior region); 10: RI 4, left posterior lung (internal region); 11: RI 5, left posterior lung (middle region); and 12: RI 6, left posterior lung (posterior region). [a]Values in kilocounts.

Table 3 - Comparison of the values of pulmonary deposition of inhaled ^{99m}Tc-tobramycin in all lung segments in phases 1 and 2 in relation to the Shwachman Score, using the paired t-test.

Shwachman Score	Lung segments	Correlation	p
Excellent/good (n = 8)	1	0.529	0.177
	2	0.538	0.169
	3	0.399	0.327
	4	−0.704	0.051
	5	0.534	0.173
	6	−0.685	0.061
	7	0.011	0.980
Moderate/fair (n = 16)	1	0.847	0.000
	2	0.826	0.000
	3	0.829	0.000
	4	0.821	0.000
	5	0.838	0.000
	6	0.825	0.000
	7	0.586	0.017

1: right anterior lung; 2: right posterior lung; 3: left anterior lung; 4: left posterior lung; 5: right lung; 6: left lung; and 7: total lungs.

Medical Sciences. All participating patients, or the parents/legal guardians of patients who were minors, gave written informed consent prior to the onset of the examinations.

Results

Twenty-seven patients were selected. Three were excluded for the following reasons, respectively: for technical difficulty in the comparison between the pulmonary areas of interest due to having been submitted to left lobectomy (reason unknown) at the age of 5; for declining to participate in the second phase of the study; and for requiring decolonization between phases. Therefore, the final sample consisted of 24 patients.

The age of the patients ranged from 5 to 27 years (mean, 12.85 ± 6.64 years), and 12 were male. Regarding the SS, 16 patients were classified as moderate/fair, 8 as excellent/good and none as severe.

The genetic analysis showed that 7 patients were ΔF508 homozygotes, 13 were ΔF508 heterozygotes, and 4 presented other mutations.

The perfusion images remained unaltered between phases 1 and 2 of the study, suggesting that there was no infection during the period.

Pulmonary deposition of the inhaled tobramycin was lower in phase 2 than in phase 1 in most areas of interest of the lungs, in the left and right lungs and in the total of the lungs ($p < 0.05$; Tables 1 and 2).

The patients with a moderate/fair SS presented lower deposition of inhaled tobramycin than did those with an excellent/good score ($p < 0.05$; Table 3).

The heterozygotes for the ΔF508 mutation also presented lower deposition of the inhaled drug than did the homozygotes and the patients with other mutations (Table 4).

Discussion

The use of IAs for the treatment of lower respiratory tract infections in patients with CF has emerged as an alternative to parenteral treatments designed to eliminate *P. aeruginosa* colonies. Locally-administered antibiotics have greater deposition at the site of infection and lower risks of systemic side effects than do parenteral therapies.

Despite their wide use, there are questions regarding the variability of the pulmonary deposition of IAs. Most studies show that the intrapulmonary obstruction and the severe forms of the CF reduce the peripheral distribution of the IAs in the lungs.[21]

One group of authors reported that children with CF present accumulation of radioaerosols in the central regions of the lungs and trachea, which was not observed in healthy individuals, probably due to the bronchial obstruction and impaired mucociliary clearance in individuals with CF.[28]Other authors have shown that the bronchopulmonary deposition of aerosols is less

Table 4 - Comparison of the values of pulmonary deposition of inhaled ^{99m}Tc-tobramycin in all lung segments in phases 1 and 2 in relation to the cystic fibrosis genotype, using the paired t-test.

Mutations	Lung segment	Correlation	p
ΔF508 homozygotes (n = 7)	1	0.749	0.053
	2	0.879	0.009
	3	0.585	0.167
	4	0.790	0.035
	5	0.817	0.025
	6	0.702	0.079
	7	0.451	0.310
ΔF508 heterozygotes (n = 13)	1	0.621	0.024
	2	0.507	0.077
	3	0.666	0.013
	4	0.664	0.013
	5	0.550	0.051
	6	0.675	0.011
	7	0.567	0.043
Other mutations (n = 4)	1	0.840	0.160
	2	0.802	0.198
	3	0.887	0.113
	4	0.856	0.144
	5	0.825	0.175
	6	0.873	0.127
	7	0.802	0.198

1: right anterior lung; 2: right posterior lung; 3: left anterior lung; 4: left posterior lung; 5: right lung; 6: left lung; and 7: total lungs.

uniform in patients with CF than in healthy individuals.[19]

Therefore, the Cystic Fibrosis Trust[29] recommends that all patients chronically colonized with *P. aeruginosa* be treated with specific IA therapy, preceded by respiratory therapy and the use of a bronchodilator to maximize the pulmonary deposition and protect from the bronchial obstruction induced by the IA.

The European consensus on antibiotic therapy against *P. aeruginosa* in CF also recommends the use of respiratory therapy, bronchodilator or mucolytic agent prior to the administration of IA to improve the bronchopulmonary deposition of the medicine.[24]

One group of authors suggested that inhaled albuterol should be used prior to the respiratory therapy, and that the IA be used thereafter.[1] Those same authors also recommended that the bronchodilator be added to the IA solution.

Despite the indiscriminate use of IAs, encouraged by consensuses and professional societies, we found no scientific studies in the literature confirming these recommendations. To our surprise and in contrast with these recommendations, we showed that the use of respiratory therapy and the administration of inhaled albuterol failed to improve the pulmonary deposition of tobramycin.

Respiratory therapy techniques have been used as adjuvants to the treatment of CF at all referral centers. Although these techniques are part of the treatment that these patients receive throughout their lives, there are no studies evaluating their efficacy in relation to the penetration of drugs in the lungs of these patients, who are of various ages and present different degrees of disease severity.

In the present study, the Flutter® device maneuver was used as a respiratory therapy technique, because it is an easily learned technique and thus allowed that a pattern be followed by all patients without interference by the professional. This technique can be used in children and presents greater adherence to its performance in the homes of the patients. In addition, it is scientifically proven to be as efficacious as is conventional respiratory therapy.[26,27] The Flutter® device produces oscillating pressure that is transmitted to the entire tracheobronchial tree, with pressure between 18 and 22 cmH_2O during normal exhalation and over 35 cmH_2O during forced exhalation. Its objective is to mobilize the mucus and remove it via the cough mechanism.[26]

Since this technique mobilizes and removes the mucus, we believe that this secretion has been detached from the small airways and impacted in the upper airways, decreasing the penetration of the IA, which was administered immediately after the Flutter® device maneuver had been performed.

It is likely that the removal of bronchial secretions is less rapid in patients with CF, since such patients present deficient or even absent mucociliary clearance, as well as since the mucus is thicker and more firmly adhered to the bronchial walls due to alteration in the rheology of the mucus.

It should be specifically noted that the patients with moderate/fair SS, that is, with more advanced pulmonary disease, presented lower pulmonary deposition than did those who presented mild pulmonary disease, showing the

restricted penetration of the IA in airways with injuries or obstruction.

Patients who were ΔF508 heterozygotes also presented lower pulmonary deposition of inhaled tobramycin. These patients were older, presented greater progression of pulmonary disease and, therefore, more severe clinical scores.

Our results raise intriguing questions that require answers for the community working with CF.

- How long after respiratory therapy should IAs be administered?
- Should patients with CF use albuterol prior to the administration of IAs?

It is currently known that IAs are efficacious in the management of pulmonary disease in patients with CF, principally in the treatment of *P. aeruginosa* colonization. However, the variability of the pulmonary deposition of the IAs has caused CF study groups worldwide to recommend the use of respiratory therapy and bronchodilators in order to increase its pulmonary deposition, even without scientific confirmation.

Our data allow us to conclude that the pulmonary deposition of ^{99m}Tc-tobramycin in patients with CF is impaired when preceded by respiratory therapy and by the use of inhaled albuterol Therefore, the use of bronchodilators and of the respiratory therapy techniques, recommended by most consensuses for the treatment of CF, merits further study in order to determine the true efficacy of using these procedures prior to the administration of the IAs.

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