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Inhaled Tobramycin and Bronchial Hyperactivity in Cystic Fibrosis

Maya Ramagopal, MD, and Larry C. Lands, MD, PhD*

Summary. The use of inhaled tobramycin for prophylaxis and treatment of respiratory symptoms in cystic fibrosis (CF) is now widespread. There have been concerns that inhaling the intravenous (I.V.) formulation of tobramycin causes bronchoconstriction. Previous studies using this formulation have either not specified the nebulizing equipment, or studied older, more severely affected patients. This study investigated the incidence of bronchoconstriction with tobramycin inhalation in children with mild to moderate CF. We studied 26 patients between the ages of 7 and 17 years, with mild to moderate CF (20 female). Prior to being placed on prolonged inhaled tobramycin therapy, they underwent a "tobramycin challenge." FEV_1 was measured pre and post challenge. For the test, standard I.V. solution (80 mg/2 mL) diluted with 2 mL of normal saline was nebulized, using the Hudson (Temecula, CA) RCI Updraft II nebulizer. The nebulization lasted 2 min. There was a 3-min "quiet period," following which FEV_1 was measured. A decrease in FEV_1 by at least 10% post-tobramycin inhalation was considered to be a positive test. Results were analyzed using the Pearson Chi-square test.

Five of 26 (19%) had a positive reaction to tobramycin. Sixteen of 26 (61.5%) were using salbutamol on a daily basis at the time of testing but not for 48 hr before the challenge, and 16 of 26 (61.5%) had a pre-tobramycin FEV_1 of $\leq$80%. Neither an FEV_1 of <80% ($P = 0.93$) nor regular use of salbutamol ($P = 0.34$) were associated with a positive tobramycin challenge.

This study suggests that, while bronchoconstriction does occur, many patients do not exhibit bronchoconstriction in response to the standard I.V. preparation and, as prior work suggests, this may be reduced further by pretreatment with salbutamol. **Pediatr Pulmonol. 2000; 29: 366–370.**

Key words: cystic fibrosis; tobramycin; bronchoconstriction; airway reactivity; antibiotic aerosol treatment.

INTRODUCTION

Pseudomonas aeroginosa is the most common bacterial pathogen associated with pulmonary exacerbations in cystic fibrosis (CF).[1] Systemic antibiotic therapy is limited by the poor penetration of most intravenously administered agents into bronchial secretions and the impairment of their biological activity by purulent secretions.[2] The aerosolized route is therefore a rational mode of delivering medications to the site of infection. Delivery of aminoglycosides by the aerosolized route to the lower respiratory tract has been advocated as a means of achieving high antibiotic concentrations at the site of infection.[3] Treatment with twice-daily aerosolized gentamicin and carbenicillin in a group of older patients with CF resulted in improved lung function and reduced hospitalizations.[4] Inhaled tobramycin at a dose of 80 mg T.I.D. appeared to have a significant effect in arresting or delaying pulmonary deterioration in some patients with CF.[5] More recently, there have been reports of a significant reduction in rates of hospitalization following the use of daily or intermittent aerosolized aminoglycosides.[6–8]

Despite the obvious advantages of inhaled antibiotics, there have been concerns regarding adverse effects. Inhalation of the standard intravenous (I.V.) preparation of tobramycin has been implicated in causing adverse effects such as bronchoconstriction, chest tightness, and cough in some CF patients.[9] While the exact mechanisms causing bronchoconstriction are not clear, several etiologies have been suggested, such as tonicity of the solution,[10] dose of the drug,[9] mode of delivery,[11] presence of additives in the solution,[9] and an inherent increase in bronchial reactivity in CF patients.[12,13]

We investigated whether the standard I.V. preparation

Department of Respiratory Medicine, Montreal Children's Hospital, Montreal, Province of Quebec, Canada.

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*Correspondence to: Dr. Larry C. Lands, Department of Respiratory Medicine, Montreal Children's Hospital, Room D-380, 2300 Tupper St., Montreal, Quebec H3H 1P3, Canada. E-mail: llanpul@mch.mcgill.ca

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of tobramycin caused adverse bronchoconstrictive effects in a group of children with CF with mild to moderate lung disease. There are only two prior studies in the literature, each with a small number of patients: one had an older, sicker population,[9] and the other[10] did not specify the type of nebulizer used during the inhalation. A preliminary report by Adeboyeku et al.[14] also found that 21% of adult CF patients had a >10% fall in FEV_1 following a first-time challenge with inhaled tobramycin. However, neither the dose of tobramycin nor the type of nebulizer were specified. The type of nebulizer used determines the particle size of the aerosol, which can impact on the frequency and severity of adverse effects.[15]

We observed that significant bronchoconstriction occurred in 19% of patients.

MATERIALS AND METHODS

Patients

Our retrospective analysis involved data on 26 patients (20 female) with CF evaluated over an 8-year period (1991–1999). All patients were being followed at the CF clinic at the Montreal Children's Hospital. The age range of the patients was 7–17 years (12.15 ± 3.02, mean ± SD). The prechallenge FEV_1 for the whole group ranged from 33–105% of predicted values (66.96 ± 21.49%). Sixteen of 26 (61.5%) had FEV_1 ≤80% predicted at the time of the challenge. At the time of testing,16/26 (61.5%) of the patients used salbutamol, either because they had previously demonstrated a bronchodilator response (>12% change in FEV_1 and/or >25% change in $FEF_{25-75\%}$) or had recurrent episodes of wheezing. Patients were on their routine dose of 2.5 mg of salbutamol twice a day prior to chest physiotherapy.

Methods

Once clinical deterioration was evident in patients colonized with sensitive *Pseudomonas aeruginosa*, the decision was made to start them on daily nebulized tobramycin. Prior to starting long-term therapy, all patients underwent a "tobramycin challenge." Patients who were using salbutamol regularly stopped taking it 48 hr prior to testing. The challenge consisted of inhaling standard I.V. tobramycin preparation (80 mg/2 mL, Nebcin™, Eli Lilly Canada, Inc., Toronto, Ontario, Canada) to which was added 2 mL of normal saline, to make a total fill volume of 4 mL (osmolality 243 mosmol·kg^{-1}).The solution was delivered via an unvented nebulizer (Hudson RCI Up-Draft II, Temecula, CA). The flow through the nebulizer was 8 L/min, driven by a source of dry, compressed air. The challenge was limited to 2 min, following which there was a 3 min "rest period."

FEV_1 was measured before and after the tobramycin challenge. The FEV_1 was measured using Sensor Medics Vmax™ series 229 equipment (Gould 5000 IV prior to 1994), in accordance with ATS criteria.[16] A >10% decrease in FEV_1 post -challenge was considered a positive reaction, to allow for comparison with previously published work.[9]

Data were analyzed using STATISTICA for Windows (Statsoft, Inc., Tulsa, OK). Statistics employed Pearson's chi-square test. Linear regression analysis was performed to ascertain the effect of prechallenge FEV_1 on the change in FEV_1 (hereafter referred to as Δ FEV_1). Differences associated with probabilities of $P < 0.05$ were considered to be significant.

Abbreviations

CF	Cystic fibrosis
Δ FEV_1	Change in FEV_1 following tobramycin challenge
FEV_1	Forced expiratory volume in 1 sec
$FEF_{25-75\%}$	Maximum mid-expiratory flow rate
I.V.	Intravenous
T.I.D.	Three times a day
VRS™	Ventolin respiratory solution (salbutamol solution)

TABLE 1—Characteristics of Positive Responders to Tobramycin Challenge[1]

Age	Gender	Prior salbutamol use	Pre-FEV_1 (%pred)	Post FEV_1 (%pred)	% change
7	Female	Yes	92	80	13
8	Female	No	105	75	28
13	Female	Yes	53	46	13
14	Female	Yes	46	39	14
17	Female	Yes	42	34	19

[1]%pred, percent of predicted.

RESULTS

Five of the 26 patients (19%) showed a >10% fall in FEV_1 following tobramycin inhalation. The characteristics of the patients who responded positively to tobramycin are shown in Table 1. There was no significant difference in Δ FEV_1 between the "on salbutamol" and "off salbutamol" groups ($P = 0.34$). Neither was there a significant difference in Δ FEV_1 if the prechallenge FEV_1 was ≤80% predicted ($P = 0.93$).

There was no significant relationship between the decrease in FEV_1 and the initial FEV_1 for the group as a whole (n = 26, $P > 0.1$), the group on salbutamol (n = 16, $P > 0.1$), and the group not on salbutamol (n = 10, $P > 0.1$) (Fig. 1).

DISCUSSION

We found that inhaling the standard I.V. preparation solution of tobramycin caused significant bronchocon-

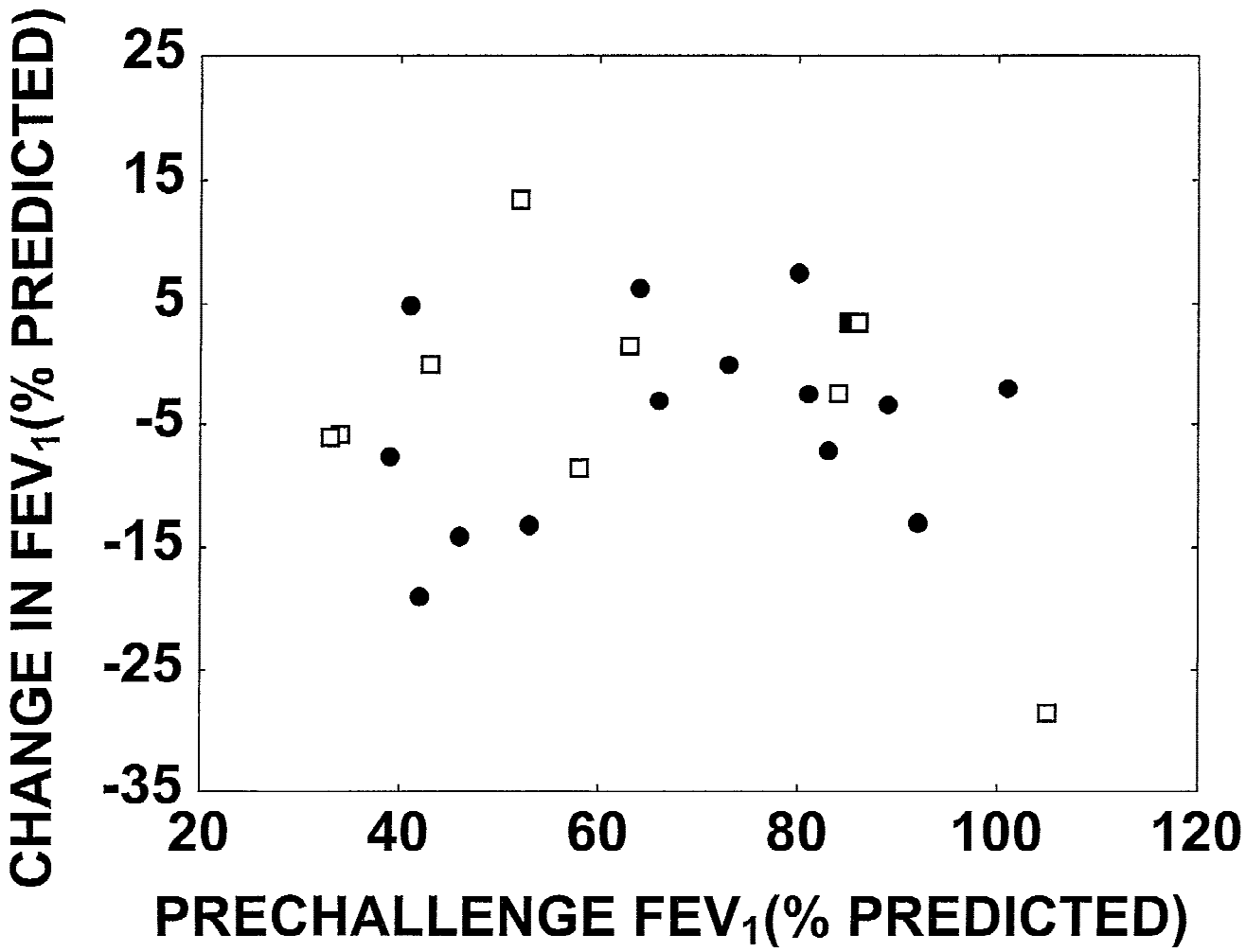

Fig. 1. Response to tobramycin challenge according to patients' prechallenge FEV_1 and salbutamol status. ●, patients routinely using salbutamol; □, patients *not* routinely using salbutamol.

striction in 5/26 patients (19%), similar to a report of young adults with more advanced disease.[9] A few studies have addressed airway reactivity with inhaled tobramycin. Exact comparisons with our study are difficult because of differences in dosages, disease severity, and ages of the patients. Chua et al.[10] studied 12 children with CF between the ages of 5–15 years. All had normal lung function (FEV_1 >80%). Tobramycin (40 mg/2 mL) did not cause a >20% decrease in FEV_1, which they considered a significant response. A drawback of their study was that the type of nebulizer used was not specified. This is important because the type of nebulizer used is one of the factors that affects drug output and particle size. A study by Coates et al.[11] has highlighted this point. In their study, the output of tobramycin aerosol was compared between two types of jet nebulizers, the gas flow through the nebulizer, and the addition of salbutamol solution (VRS™) to the solution. They concluded that the Hudson 1730 nebulizer (as was used in this study) and the addition of a commercial salbutamol solution VRS™ to the solution resulted in the largest amount of drug delivered in the respirable fraction (1–5 μm in diameter).

Particle size is directly related to adverse effects. Particles greater than 5 μm in diameter cause cough as a result of inertial impaction at the level of the posterior pharynx. Particles less than 1 μm in diameter carry little drug and may be exhaled. Hence, the volume or mass of drug contained in particles between 1–5 μm in diameter have the highest likelihood of being deposited in the lungs.[17] The relatively high flow (8 L/min) used in the present study would be expected to result in an increased delivery of medication to the lower airways, compared to the flow from a portable compressor.[11] This may have increased the incidence or severity of observed bronchoconstriction.

Chua et al.,[10] while addressing the tonicity of a solution as being one of the factors responsible for adverse effects, found that tobramycin (osmolality 248 mosmol·kg^{-1}) was relatively hypotonic compared to ticarcillin

(osmolality 3,080 mosmol·kg^{-1}) and normal saline (osmolality 272 mosmol·kg^{-1}). No patient had a >10% fall in FEV_1 after inhalation of tobramycin, compared to 5/12 after ticarcillin and 1/12 after normal saline. The osmolality of the tobramycin preparation used in the present study was 243 mosmol·kg^{-1}, comparable to that used by Chua et al.[10]

The additives in the standard I.V. tobramycin preparation, such as antioxidants (EDTA and sodium metabisulphate, 1.44 mg) and the preservative phenol (5 mg), have been implicated in causing adverse effects such as bronchoconstriction, chest tightness, and cough.[9] However, even a more recent preservative-free formulation of tobramycin (osmolality 158–183 mosmol·kg^{-1}) caused bronchoconstriction in some patients.[8]

Prior treatment with salbutamol reduces the incidence of bronchoconstriction induced by nebulized tobramycin. Nikolaizik et al.[9] studied 12 older patients (mean age 22.6 years) with relatively advanced disease (mean FEV_1 = 49%, mean room air saturation = 88%). After inhalation of the tobramycin preparation with preservatives and a tobramycin concentration of 80 mg/4 mL (as was used in this study), 3/12 (25%) had a >10% decrease in FEV_1. Pretreatment with 4 puffs (0.4 mg) of salbutamol resulted in no patient demonstrating a >10% decrease in FEV_1.[9]

It is common clinical practice in some CF centers to combine salbutamol and tobramycin in the same nebulizing solution. The rationale for this is twofold: first, airways narrowed by bronchospasm could be dilated to improve pulmonary distribution of the drug, and second, simultaneous administration of the medications saves time.

Nikolaizik et al.[9] also reported that normal saline produced a significant fall in FEV_1 in 5/12 patients. Note that this incidence is higher than that reported by Chua et al.,[10] but these patients had more advanced disease (mean FEV_1 49% vs. >80%). This is in agreement with Mellis et al.,[12] who found positive responses to histamine in 24% of their CF patients. They suggested that this is due to the lowered threshold of stretch ("irritant") receptors in the airway epithelium, causing an exaggerated response to histamine. None of the patients with normal lung function had a positive response to histamine, implying that extensive lung damage is necessary for the lowering of the threshold of stretch receptors. Similarly, Boushey et al.[13] suggested that bronchial hyperactivity in CF could be due to epithelial damage causing increased airway permeability, allowing higher concentrations of inhaled materials to reach "target" cells like smooth muscles and sensory nerves.

In our patients who showed a positive response to inhaled tobramycin, we recommended that they continue to use it with the addition of salbutamol to the solution. Addition of VRS™ lowers the surface tension of the solution due to the presence of the preservative benzalkonium chloride and this results in greater drug output.[18] It should be noted that the addition of 0.5 mL of VRS™ (5 mg/mL) and 1.5 mL of normal saline to 80 mg/2mL of tobramycin (as opposed to the nebules which are preservative-free) resulted in better nebulization without significantly affecting the osmolality of the solution (242 mosmol·kg^{-1}). We did not, however, retest patients on this combination.

The majority of our patients use a disposable jet nebulizer for aerosolizing antibiotics at home. This is consistent with reports from other centers.[19] Routine use of a breath-enhanced nebulizer, such as the Pari LC Plus™ nebulizer, would be additionally beneficial; minimal drug is lost during exhalation and more is nebulized during inhalation. This results in doubling the amount of drug nebulized relative to the unvented nebulizers.[15] This is the type of nebulizer that was used by Nikolaizik et al.[9]

In conclusion, while bronchoconstriction is a potential side effect of inhaling standard I.V. tobramycin, most patients (19/26) demonstrated less than a 10% decrease in FEV_1 in response to the inhalation of the intravenous preparation of tobramycin. Even in patients who demonstrated a positive response, we continued to use it with the addition of salbutamol to the solution. Although patients were not rechallenged on this combination, they reported continued use without further problems. Heightened bronchial reactivity in CF patients is a likely contributor to the positive tobramycin challenges in our patients.

We feel that inhalation of the standard I.V. preparation of tobramycin may be indicated as long-term therapy for slowing lung deterioration in CF patients.

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REFERENCES

1. Hoiby N, Flensborg EW, Beck B, Friis B, Jacobsen SV, Jacobsen L. *Pseudomonas aeroginosa* infection in cystic fibrosis. Scand J Respir Dis 1997;58:65–79.
2. Mendelman PM, Smith AL, Levy J, Weber A, Ramsey B, Davis RL. Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. Am Rev Respir Dis 1985;132:761–765.
3. MacLusky I, Levison H, Gold R, McLaughlin FJ. Inhaled antibiotics in cystic fibrosis: is there a therapeutic effect? J Pediatr 1986;108:861–865.
4. Hodson ME, Penketh AR, Batten JC. Aerosol carbenicillin and gentamicin treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis. Lancet 1981;2:1137–1139.
5. MacLusky IB, Gold R, Corey M, Levison H. Long-term effects of inhaled tobramycin in patients with cystic fibrosis colonized with *Pseudomonas aeruginosa*. Pediatr Pulmonol 1989;7:42–48.

6. Stead RJ, Hodson ME, Batten JC. Inhaled ceftazidime compared with gentamicin and carbenicillin in older patients with cystic fibrosis infected with *Pseudomonas aeruginosa*. Br J Dis Chest 1987;81:272–279.
7. Wall MA, Terry AB, Eisenberg J, McNamara M, Cohen R. Inhaled antibiotics in cystic fibrosis [letter]. Lancet 1983;1:1325.
8. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, Vasiljev K-M, Borowitz D, Bowman CM, Marshall BC, Marshall S, Smith AL, Cystic Fibrosis Inhaled Tobramycin Study Group. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. N Engl J Med 1999;340: 23–30.
9. Nikolaizik WH, Jenni-Galovic V, Schoni MH. Bronchial constriction after nebulized tobramycin preparations and saline in patients with cystic fibrosis. Eur J Pediatr 1996;155:608–611.
10. Chua HL, Collis GG, Le Souef PN. Bronchial response to nebulized antibiotics in children with cystic fibrosis. Eur Respir J 1990; 3:1114–1116.
11. Coates AL, MacNeish CF, Meisner D, Kelemen S, Thibert R, MacDonald J, Vadas E. The choice of jet nebulizer, nebulizing flow, and addition of albuterol affects the output of tobramycin aerosols. Chest 1997;111:1206–1212.
12. Mellis CM, Levison H. Bronchial reactivity in cystic fibrosis. Pediatrics 1978;61:446–450.
13. Boushey HA, Holtzman MJ, Sheller JR, Nadel JA. Bronchial hyperreactivity. Am Rev Respir Dis 1980;121:389–413.
14. Adeboyeku DU, McKenzie D, Hodson ME. A review of one years' data of first dose challenges of inhaled antibiotics in adults CF patients. Pediatr Pulmonol [Suppl] 1999;17:405.
15. Coates AL, MacNeish CF, Lands LC, Meisner D, Kelemen S, Vadas EB. A comparison of the availability of tobramycin for inhalation from vented vs. unvented nebulizers. Chest 1998;113: 951–956.
16. American Thoracic Society. Standardization of spirometry: 1994 update. Am J Respir Crit Care Med 1995;152:1107–1136.
17. Brain JD, Valberg PA. Deposition of aerosol in the respiratory tract. Am Rev Respir Dis 1979;120:1325–1373.
18. MacNeish CF, Meisner D, Thibert R, Kelemen S, Vadas EB, Coates AL. A comparison of pulmonary availability between Ventolin (albuterol) nebules and Ventolin (albuterol) respirator solution. Chest 1997;111:204–208.
19. Rosenfeld M, Emerson J, Astley S, Joy P, Williams-Warren J, Standaert TA, Yim DL, Crist D, Thykkuttathil M, Torrence M, FitzSimmons S, Ramsey B. Home nebulizer use among patients with cystic fibrosis. J Pediatr 1998;132:125–131.