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Nebulized tobramycin: Prevention of pneumonias in patients with severe cerebral palsy

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Abstract. *Background and methods:* In patients with severe cerebral palsy, pneumonias are a frequent occurrence and can lead to excessive morbidity and mortality. Similar poor outcomes can occur in patients with cystic fibrosis. Nebulized tobramycin has been shown to be effective in preventing pneumonias, and in improving lung function in cystic fibrosis patients. This study reports results from three patients with severe cerebral palsy who were suffering from recurrent pneumonias. We compared the 12 months prior to starting nebulized tobramycin, to the first 12 months of intermittent therapy (28 days of nebulized antibiotic, followed by 28 days with no antibiotic, then repeated). We noted the number of pneumonias, the number of hospitalizations due to pneumonia, and length of hospitalizations for pneumonia.
Results: Adding the results from the three patients together, the number of pneumonias went from 19 during the year prior to starting the nebulized tobramycin, to 11 during the year of treatment. The number of hospitalizations for pneumonia went from 11 to 0. The number of days in hospital for pneumonia went from 110 to 0.
Conclusion: As in cystic fibrosis patients, patients with severe cerebral palsy may benefit from the intermittent use of nebulized tobramycin to prevent pneumonias and hospitalizations due to pneumonia. Further studies are warranted.

Keywords: Nebulized tobramycin, cerebral palsy, pneumonia

1. Introduction

Recurrent pneumonias are a common cause of illness in patients with severe cerebral palsy. Neuromuscular insufficiency produces inadequate clearance of pulmonary secretions. Our own survival rate data has shown that up to 75% of deaths in this population are due to pneumonias [5,6]. Cystic fibrosis patients also frequently have recurrent pneumonias as a major medical problem. The use of intermittent nebulized tobramycin has been shown to be of benefit to these patients in preventing pneumonia and in improving lung function [1–4,8]. Also, nebulized tobramycin has been reported to potentially be of benefit in treating bronchiectasis and ventilator-associated pneumonia (reviewed in reference 3).

We identified three severely cerebral palsied patients who were having recurrent pneumonias and were being frequently hospitalized due to pneumonia. We treated these individuals with inhaled tobramycin (TOBI, Novartis) in an attempt to decrease the number of pneumonias and hospitalizations due to pneumonia.

2. Materials and methods

Marklund Children's Home is a residential center for 26 children and young adults with severe cerebral palsy. Three residents had developed recurrent severe pneumonias that frequently required hospitalization. Data was collected prospectively for 12 months when the

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nebulized tobramycin program was started. The previous 12 months of clinical information was abstracted retrospectively from the nursing and medical records. Pneumonia was diagnosed on the basis of clinical findings, which included fever, purulent pulmonary secretions, increased oxygen requirements, and abnormalities on pulmonary examination (such as rales, rhonchii and wheezes). Patients were monitored continuously with pulse oximetry, and frequent vital signs. If they required systemic antibiotics to treat a pulmonary infection, the tobramycin nebulizers were temporary halted. When they became clinically unstable, they were sent to the local hospital emergency room for evaluation and admission. Chest X-rays were only obtained during hospitalization. In all cases, in-hospital chest X-rays confirmed the clinical diagnosis of pneumonia by showing consolidations and/or infiltrates.

Nebulized tobramycin (TOBI, Novartis) was administered in a dose of one vial, 300 mg tobramycin in 5 ml, twice a day, passively by facemask, using a jet nebulizer manufactured by Salter. It was administered daily for 28 days, then discontinued for 28 days, and the cycle repeated. Each nebulized administration took 15 minutes.

This study was approved by the Ethics Committee of Marklund Children's Home. Informed consent was obtained from the patient's guardians prior to starting this treatment program.

3. Results

3.1. Case A

Case A is a 15-year-old male with Cerebro-Oculo-Facio-Skeletal (COFS) Syndrome, severe spastic quadriplegia, and epilepsy. He was totally immobile and incontinent, with profound mental retardation and no functional hand use. He was fed by gastrostomy tube, and had a tracheostomy tube for pulmonary toilet. His systemic medications included phenobarbital, clorazepate, ranitidine, and metoclopramide. He received albuterol nebulizers (2.5 mg in 3 ml normal saline, 6 times per day), ipratropium bromide nebulizers (one vial 0.02% solution, 4 times per day), and Pulmicort respules by nebulizer (0.25 mg in 2 ml, twice per day). During the 12 months prior to starting treatment with nebulized tobramycin, and during the treatment program, there were no significant changes in systemic and nebulized medications. There were no side effects due the use of the nebulized tobramycin.

In the 12 months prior to starting therapy, he had 5 pneumonias, and was hospitalized 2 times for a total of 20 days of hospitalization. During the 12 months of therapy, the number of pneumonias decreased to 3 with no hospitalizations for pneumonia.

3.2. Case B

Case B is a 13-year-old girl with agenesis of the corpus callosum, microcephaly, severe spastic quadriplegia, and epilepsy. She was totally immobile and incontinent, with profound mental retardation and no functional hand use. She was fed by gastrostomy tube. Her systemic medications included valproic acid, clonazepam, and ranitidine. She received albuterol nebulizers (0.083% solution, 1 vial, 4 times per day). She received vest therapy [7] twice a day for 10 minutes each time. During the 12 months prior to starting treatment with nebulized tobramycin, and during the treatment program, there were no significant changes in systemic and nebulized medications, or in the use of vest therapy. There were no side effects due the use of the nebulized tobramycin.

In the 12 months prior to starting therapy, she had 9 pneumonias, and was hospitalized 4 times for a total of 24 days of hospitalization. During the 12 months of therapy, the number of pneumonias decreased to 6 with no hospitalizations for pneumonia.

3.3. Case C

Case C is a 24-year-old male who had suffered recurrent intraventricular hemorrhages and required the placement of a ventriculo-peritoneal shunt. He was totally immobile and incontinent, with profound mental retardation and no functional hand use. He was fed by gastrostomy tube, and had a tracheostomy tube for pulmonary toilet. His systemic medications included phenobarbital, diphenylhydantoin, chlorazepate, baclofen, ranitidine, and levothyroxine. He received albuterol nebulizers (2.5 mg in 3 ml normal saline, 6 times per day) and ipratropium bromide nebulizers (one vial 0.02% solution, 6 times per day). He received vest therapy [7] twice a day for 10 to 20 minutes each time. During the 12 months prior to starting treatment with nebulized tobramycin, and during the treatment program, there were no significant changes in systemic and nebulized medications, or in the use of vest therapy. There were no side effects due the use of the nebulized tobramycin.

In the 12 months prior to starting therapy, he had 5 pneumonias, and was hospitalized 5 times for a total of 66 days of hospitalization. During the 12 months of therapy, the number of pneumonias decreased to 1 with no hospitalizations for pneumonia. Of note is that during the 12 months prior to treatment with tobramycin, he required an average of 10 to 15 liters per minute of supplemental oxygen to maintain his oxygen saturation. During the treatment program, his oxygen requirement stabilized at 3 liters per minute.

4. General considerations

Ventilators are not used at Marklund, thus the patients with tracheostomies were not ventilator-dependent. As per our protocol at Marklund [7], the frequency of vest-therapy was not changed when symptoms of pulmonary infection appeared. Prior to starting the tobramycin nebulizer program, the primary antibiotic used to treat pulmonary infections at Marklund was zithromax. After starting the nebulized tobramycin, only zithromax was used to treat diagnosed pneumonias. Tracheal cultures revealed the primary causative organisms of pulmonary infections to be pseudomonas aeruginosa and proteus mirabilis. Occasional other organisms were klebsiella pneumonia and serratia marcescens. Before and during the treatment program, there was no change in the spectrum of bacterial organisms or in their antibiotic sensitivities. In particular, during the 12 months of treatment, no new antibiotic resistant strains of organisms appeared. Also, there was no increase in antibiotic resistance strains of bacteria in the other Marklund residents. Audiometric testing was done at bedside by an audiologist, and during the treatment program there was no change in hearing acuity. Renal function tests were performed every six months, and there was no change in blood test results during the treatment program. Serum tobramycin levels were not evaluated.

5. Summary

Combining the data from Cases A through C together, when comparing the preceding 12 months with 12 months of treatment, the nebulized tobramycin program resulted in a decrease in the total number of pneumonias from 19 to 11, the number of hospitalizations due to pneumonia was decreased from 11 to 0, and the number of days in hospital due to pneumonia was decreased from 110 to 0.

6. Discussion

As with patients with cystic fibrosis, individuals with severe cerebral palsy may suffer from recurrent pneumonias, many of which require hospitalization. In our experience, 75% of deaths in these disabled individuals are due to pneumonia [5,6]. In cystic fibrosis the basic problem is the tenacious property of the pulmonary secretions secondary to mutations in the CFTR gene. In severe cerebral palsy, especially in those cases that require tracheostomy tubes, the basic problem is inadequacy of neuro-muscular control of the coughing mechanism to clear pulmonary secretions. In our study, 2 of the 3 patients had tracheostomy tubes. Previously, we had shown that oscillating vest-therapy is of benefit in preventing pneumonias in severe cerebral palsy patients [7].

Our study has shown that a program of nebulized tobramycin can significantly reduce the incidence and severity of pneumonias in patients with severe cerebral palsy, which is also the case with cystic fibrosis [1–4,8]. Also, in Case C, with a significant decrease in oxygen requirements during nebulized toramycin treatment, his pulmonary status improved, as has been reported in cystic fibrosis patients [2]. In our study, the nebulization program was effective without any side effects. In particular, there was no increase in antibiotic resistant strains of bacteria in these 3 patients, nor in the other residents.

In addition, the use of nebulized tobramycin in cystic fibrosis patients has been shown to decrease over-all medical care costs [9]. In our study, the dramatic reduction in days of hospitalization from 110 to 0, most of which were intensive care unit days, has clearly resulted in substantial medical care cost savings. For our vest therapy program [7] we determined the daily average cost of a pneumonia hospitalization for our patients to be $8,225 [10]. Using this data, the hospitalization cost savings from the tobramycin nebulizer treatment program was $904,750. The current full pharmacy cost of a 28 day course of treatment with TOBI is $969 (Osco Drugs, Chicago). For our treatment of 3 cerebral palsied children, for one year, the full pharmacy cost of the nebulized tobramycin was $17,442. Thus, for every $1 invested in the tobramycin nebulizer program, $50 in medical cost savings was realized.

Further studies with larger numbers of cerebral palsied patients are indicated.

Conflict of interest

The authors report no conflict of interest.

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