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Vestibulotoxicity in a patient without renal failure after inhaled tobramycin☆

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ABSTRACT

Aminoglycoside antibiotics have a long history of use in the control of gram-negative bacterial infections, but their systemic use has been complicated by known ototoxicity and nephrotoxicity. Because of the utility of these medications in patients with frequent pulmonary infections, there has been a move towards the use of inhaled agents, in particular tobramycin, due to a lower rate of systemic complications. Inhaled tobramycin is generally consider to be safe from otologic complications, with only two previous reports of ototoxicity, both in patients who had underlying chronic renal disease. Here we present the first case of a patient developing isolated vestibular toxicity, without associated hearing loss or evidence of renal insufficiency, in a patient receiving inhaled tobramycin. This is an extremely rare complication of an inhaled aminoglycoside and underscores the importance of careful monitoring despite perceived safety.

1. Introduction

Aminoglycosides are potent class of antibiotics with a long history of use for treatment of severe gram-negative bacterial infections [1]. However, widespread use of these medications has been limited by known complications of ototoxicity and nephrotoxicity [2–4]. Each member of the aminoglycoside class of antibiotics has varying degree of selective toxicity towards the cochlea versus the vestibule. Drugs such as gentamicin, tobramycin, dibekacin are thought to be primarily vestibulotoxic while drugs like kanamycin, amikacin, and neomycin are predominantly cochleotoxic [5]. As a result if these toxicities, and difficulty in safe dosing, therapeutic approaches have been developed for the inhaled administration of these agents for the treatment of some chronic pulmonary infections. Based upon two randomized trials of inhaled tobramycin in Cystic Fibrosis (CF) patients with pseudomonal infections, the Food and Drug Administration approved this route of administration in 1997 [6]. During the approval studies, a total of 258 patients received inhaled tobramycin with no evidence of changes in audiometric testing, vestibular symptoms, or evidence of permanent impairments in renal function, as measured by changes in creatinine levels [7]. Reported side effects in the original studies were limited to tinnitus in 8 patients and voice changes in 33 patients. Serum levels of tobramycin were found to be undetectable and there was no evidence of systemic accumulation of the drug over the course of treatment [8,9]. Due to the reassuring safety profile of inhaled tobramycin in the original studies, routine monitoring has not traditionally been performed on patients undergoing therapy. Since approval, providers have used inhaled tobramycin in an off-label fashion to treat chronic bronchiectasis unrelated to CF based upon several smaller studies showing efficacy and safety [10,11].

Despite the initial evidence of safety for the use of inhaled tobramycin, there has since been and handful of cases of toxicity. There have been two reported cases of patients suffering a vestibular toxicity after receiving inhaled tobramycin. Both patients had underlying renal insufficiency, which worsened while in treatment, suggesting the possibility that there may have been systemic accumulation of the drug to levels sufficient to cause otologic toxicity [12,13]. Additionally, there is one report of a child with CF and chronic renal failure who developed profound sensorineural hearing loss after inhaled tobramycin treatment [14]. There are also two known cases of patients developing isolated acute renal failure while receiving this treatment [15,16]. Both of these patients had clinically detectable serum levels of tobramycin. Although inhaled tobramycin is still considered safe in the setting of normal renal function, we here describe the case of a patient who developed profound vestibular toxicity without evidence of concurrent cochleotoxicity or nephrotoxicity or pre-existing renal insufficiency.

2. Case report

A 75 year old Caucasian male who was a former smoker with a past

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medical history significant for rheumatoid arthritis, emphysema, bronchiectasis, interstitial lung disease, and obstructive sleep apnea presented to the Lung Center for management of his dyspnea, cough, and fever going on for two weeks. He had no pre-existing history of renal impairment or balance difficulties, but did note a history of non-bothersome, subjectively mild hearing loss. Pulmonary symptoms improved, but did not resolve following initial treatment with a 14-day course of doxycycline. Sputum cultures grew *P. aeruginosa* which was sensitive to levofloxacin and tobramycin. After unsuccessful treatment with of oral levofloxacin, he was started on inhaled tobramycin 300 mg twice a day for planned 28-day course using a jet nebulizer. Shortly after beginning treatment, the patient developed progressive imbalance to such a degree that he was unable to ambulate without a cane, which he never previously had to use. Laboratory tests were drawn by his pulmonologist to monitor for possible toxicity, and the patient was found to have a creatinine of 1.26, considered to be consistent with absence of any nephrotoxicity. Prior to the initiation of treatment his creatinine varied from 0.95 to 1.28. Although his pulmonary symptoms improved on the inhaled tobramycin, treatment was discontinued to avoid further vestibular insult.

The patient's symptoms did not improve following cessation of therapy, and he was referred to our vestibular clinic for further evaluation. At the time of initial evaluation, the patient endorsed non-vertiginous dizziness when walking but declined ever having experienced rotary vertigo, oscillopsia, or visual slip. His audiogram showed bilateral high-frequency sloping sensorineural hearing loss with word recognition scores of 84%, although the patient noted that his subjective hearing had not changed as a result of the tobramycin exposure (Fig. 1). On physical exam, he was noted to have a normal otologic examination. Vestibular exam show no spontaneous or gaze-evoked nystagmus, however rapid head thrust testing in the horizontal plane demonstrated bilateral catch-up saccades, and he was noted to have a wide-based gait. He underwent vestibular testing which demonstrated absent nystagmus, but caloric testing showed bilateral reduced vestibular function with left ear responses to warm/cool irrigations of 0 and 4 degrees per second, and 2 and 4 on the right. Ice water calorics were not performed and video head impulse testing (vHIT) was not available at that time. Rotary chair testing of the vestibular-ocular reflex showed reduced gains with phase leads and asymmetry of left greater than right. Moreover during computerized dynamic posturography he showed poor balance function and falls in vestibular-isolating conditions with vision denied.

An MRI of the brain and internal auditory canal with gadolinium contrast did not reveal any pathology. The patient was treated vestibular rehabilitation which allowed him to make slow improvements over the subsequent three years such that he no longer needed a cane to ambulate. He has reported no further declines in his vestibular function over that same time period.

3. Discussion

Until now there have only been 5 reported instances of ototoxicity or nephrotoxicity induced from inhaled tobramycin. All the prior cases had underlying renal disease or developed renal disease while being treated. Herein, we report the first instance of ototoxicity in a patient with normal renal function and who did not subsequently develop renal failure. All prior cases had patients with significantly elevated creatinine potentially giving a mechanism for toxicity to develop while our patient's creatinine remained in the normal range and was not significantly elevated from his baseline. This patient had isolated vestibular toxicity without having measurable changes in his cochlear function which is consistent with the primarily vestibulotoxic effects of tobramycin.

However, in order for a patient to develop ototoxicity, there must be sufficient systemic accumulation to allow toxic concentrations within the cochlear or vestibular end organs. To what extent this occurred in the present case is unclear. As the indications for inhaled tobramycin have broadened over the years, the original papers showing no accumulation in CF patients may not reflect these risks to all patient receiving treatment. Compared to patients with bronchiectasis patients with CF have thicker mucus with increased amount of glycoproteins which can directly bind the drug, possibly limiting systemic exposure [22,23]. Moreover, the sputum found in patients with CF differs from that of isolated bronchiectasis in that it has decreased pH and increased divalent cations which in vitro has lead to reduced levels [24].

An additional factor that can contribute to systemic accumulation is the method of aerosolization and delivery. Newer nebulizers have been shown lead to double the concentration of drug in the sputum [25]. Furthermore, positive pressure or jet nebulization can also lead to toxic accumulation of inhaled tobramycin [26].

The exact mechanism by which tobramycin and other aminoglycoside antibiotics exerts their ototoxic effects is still unclear. Currently thinking is that tobramycin induces the creation of reactive oxygen species which damages the hair cells within the cochlea and vestibule [3,17]. Alternatively, tobramycin can bind to NMDA receptors leading to their activation and resulting glutamate excitotoxicity [18,19]. Normally, tobramycin is unable to bind to and inhibit human ribosomes however approximately 1 in 500 people of European descent have a

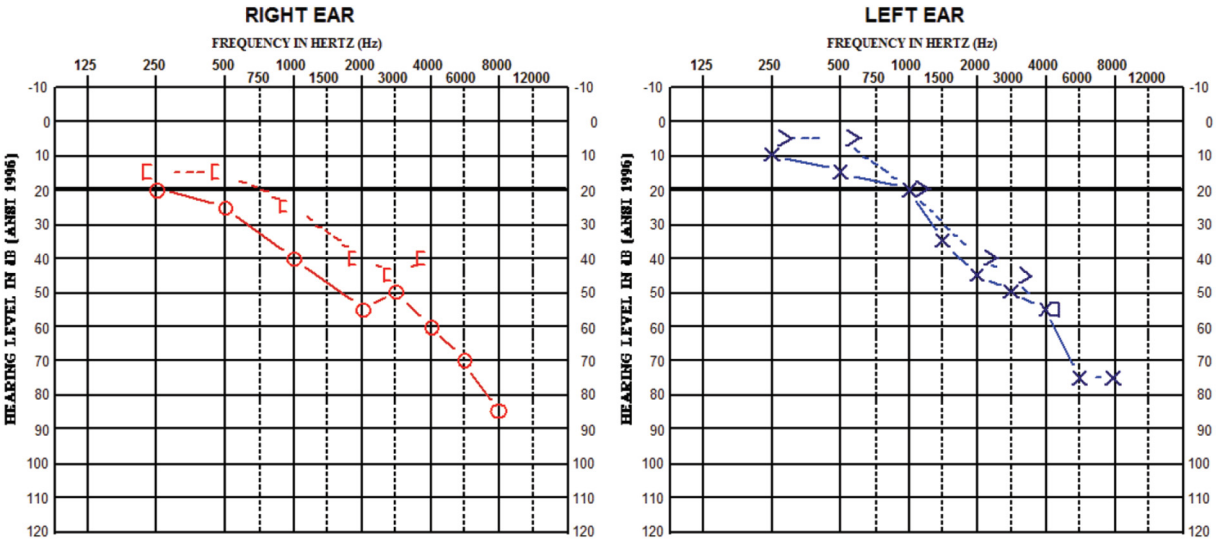

Fig. 1. Post-tobramycin treatment audiogram showing symmetric high frequency hearing loss although it is unclear if this was present prior to treatment.

point mutation in their 12S ribosome allowing tobramycin to inhibit cellular protein production [20,21].

Besides once daily dosing and serum monitoring there are few effective strategies to protect against the development of ototoxicity while treating with aminoglycosides. Currently it is not cost effective to screen all patients receiving aminoglycosides for the ribosomal point mutation. Using antioxidants, such as *N*-acetylcysteine (NAC) or salicylate, to protect against reactive oxygen species have been shown to significantly reduce toxicity from gentamicin [27–29]. NAC has shown a similar otoprotective effect in patients treated with amikacin [30].

It remains to be seen why this patient uniquely developed sequelae while the vast majority of patients have been able to use inhaled tobramycin with minimal off-target effects for over twenty years. Nonetheless, it is essential to keep in mind this possibility when starting patients on this form of treatment. If the patient has a family history of toxicity, it may be useful to consider genetic screening and serum monitoring.

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