Vestibular Toxicity Due to Inhaled Tobramycin in a Patient With Renal Insufficiency

RANDALL S. EDSON, MD; ROBERT H. BREY, PHD; THOMAS J. MCDONALD, MD; CHRISTINE L. TERRELL, MD; JAMES T. MCCARTHY, MD; AND JANET M. THIBERT, MS

Inhaled tobramycin is being used increasingly in patients with cystic fibrosis and other forms of bronchiectasis for treatment of bronchial colonization with *Pseudomonas aeruginosa*. The goal of inhaled antibiotics is to provide maximal concentrations at the site of infection without risking systemic toxicity. We report an unusual case of reversible vestibular toxicity due to inhaled tobramycin in a patient with renal failure who was undergoing hemodialysis. Although systemic absorption after inhaled tobramycin is reportedly negligible, no recommendations have been published regarding monitoring of serum concentrations in patients receiving this form of therapy. We suggest that clinicians consider monitoring serum concentrations of tobramycin in patients at risk of renal toxicity and/or ototoxicity, such as those with predisposing renal or otologic compromise. Further studies in at-risk patients are needed to determine the optimal frequency and timing of such monitoring.

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Inhaled tobramycin was approved by the US Food and Drug Administration in 1997 for the treatment of pulmonary infections caused by *Pseudomonas aeruginosa* in patients with cystic fibrosis. Approval was based on 2 randomized trials[1] that showed that recipients of intermittent inhaled tobramycin had improved pulmonary function, decreased density of *P aeruginosa* in sputum, and reduced duration of hospitalization compared with patients who received placebo. The median serum concentration of tobramycin was 0.94 mg/L (range, <0.18-3.62 mg/L). None of the 252 patients studied experienced renal or eighth nerve toxicity, although 8 patients reported transient tinnitus in the absence of hearing loss; the drug was not discontinued in any of these patients. Patients with compromised renal function (defined as a serum creatinine level of ≥2 mg/dL) were excluded from these studies. We report a patient with renal insufficiency in whom inhaled tobramycin caused overt vestibular toxicity.

From the Division of Infectious Diseases and Internal Medicine (R.S.E., C.L.T.), Vestibular/Balance Laboratory (R.H.B., J.M.T.), Department of Otorhinolaryngology (T.J.M.), and Division of Nephrology and Hypertension and Internal Medicine (J.T.M.), Mayo Clinic College of Medicine, Rochester, Minn.

Individual reprints of this article are not available. Address correspondence to Randall S. Edson, MD, Division of Infectious Diseases, Mayo Clinic College of Medicine, 200 First St SW, Rochester, MN 55905 (e-mail: edson.randall@mayo.edu).

REPORT OF A CASE

A 41-year-old woman who was undergoing hemodialysis for chronic renal failure due to Wegener granulomatosis experienced bronchiectasis with chronic *P aeruginosa* colonization that was complicated by frequent episodes of symptomatic bronchopneumonia. Repeated courses of parenteral antimicrobial therapy and hospitalization were required. At evaluation on May 11, 1999, the patient was afebrile. Physical examination disclosed crackles at the right lung base but no other abnormal findings. Laboratory studies revealed a white blood cell count of 4.6×10^9/L and a serum creatinine level of 9.2 mg/dL; sputum culture yielded a heavy growth of *P aeruginosa*. Chest radiography showed scarring in the right lung base, and computed tomography revealed bronchiectasis.

In an attempt to reduce the density of *P aeruginosa* in the sputum, the patient was treated with inhaled tobramycin, 300 mg twice daily, beginning on May 12, 1999. On May 28, the serum tobramycin level was 19.2 mg/L, and on June 5, it was 19.5 mg/L. On both occasions, tobramycin levels were obtained before hemodialysis. Because of the considerably elevated serum concentrations, inhaled tobramycin was discontinued, and the predialysis serum concentration decreased to 9.8 mg/L 2 days later. One week after use of tobramycin had been discontinued, the patient experienced dizziness, ataxia, and oscillopsia.

The patient was initially referred for auditory and vestibular testing on July 2, 1999, and underwent follow-up assessments on August 21, 2002, and March 11, 2003. The Dizziness Handicap Inventory[2] was administered to determine the patient's level of handicap. This inventory consists of 25 questions that address the physical, emotional, and functional components of a patient's complaints. Seven questions focus on physical aspects (eg, "Does bending over increase your problem?"), 9 address emotional issues (eg, "Because of your problem, do you feel handicapped?"), and 9 relate to functional limitations (eg, "Because of your problem, is it difficult for you to go for a walk by yourself?"). Each question has a score of 0, 2, or 4 for answers of "No," "Sometimes," and "Yes," respectively. Higher scores indicate greater handicap. In 1999,

TABLE 1. **Results of Dizziness Handicap Inventory in a Patient With Inhaled Tobramycin–Associated Vestibular Toxicity***

	Component Scores			
	Physical	Emotional	Functional	Total score
July 1999	26/28	20/36	26/36	72/100
March 2003	8/28	10/36	8/36	26/100
Improvement (points)	18	10	18	46

*See text for explanation of scoring.

our patient's total score was 72, which is extremely high and indicates major difficulty. Four years later, her score was 26, a marked decrease in perceived handicap, but she continued to experience some disability (Table 1). In 1999, vestibular rehabilitation was recommended, but in 2003, the patient reported that she had not undergone therapy because her insurance provider did not cover the cost.

Pure-tone air-conduction thresholds were measured in 1999 and 2002. In 1999, the patient had mild high-frequency hearing loss at 6 and 8 kHz (Figure 1, left). In 2002, hearing sensitivity was normal from .25 kHz through 8 kHz bilaterally (normal, 0-25 dB) (Figure 1, right).

Eye movements were measured with use of electro-oculography. Gaze testing with the eyes open and fixed at ±30° horizontal and vertical produced no nystagmus. Smooth ocular pursuit results in 1999 and 2002 were within normal limits, based on ICS reference values (ICS Medical, Schaumburg, Ill). Figure 2 (top) shows the normative and mean patient data for frequencies 0.2 to 0.7 Hz measured in 1999. Careful scrutiny of the smooth pursuit at 0.71 Hz in 1999 (Figure 2, top, upper panel between vertical lines) revealed a definite cogwheel or stair-stepping pattern for pursuit. This pattern is usually seen with some type of central nervous system dysfunction. By August 2002, cogwheeling was no longer evident (Figure 2, bottom, upper panel).

Horizontal saccadic eye movement testing in 1999 and 2002 revealed normal velocities, accuracies, and latencies.

Positional testing was done with the patient's eyes closed, and she performed a mental alerting task to keep the brain from suppressing nystagmus. Nystagmus indicated a bias difference between the 2 ears, with the patient in the sitting, supine, head-right, head-left, head-hanging, and 30° supine position (Table 2). Right-beating nystagmus was noted in 5 of 6 head positions tested in 1999. In 2002, the patient had nystagmus in only 3 of the 6 head positions. Although these findings were considered nonlocalizing, they showed a reduction in the bias difference between the ears and highlight the importance of monitoring positional nystagmus to document changes that have occurred over time.

Bithermal binaural caloric testing, the gold standard for assessing any difference in strength between the ears as well as the overall strength of the responses, was performed in 1999 and 2002 (Figure 3). In 1999, total absolute responses to warm and cool irrigations of the right and left ear were 20° per second and 24° per second, respectively, for a total of 44° per second in both ears (Figure 3, top).

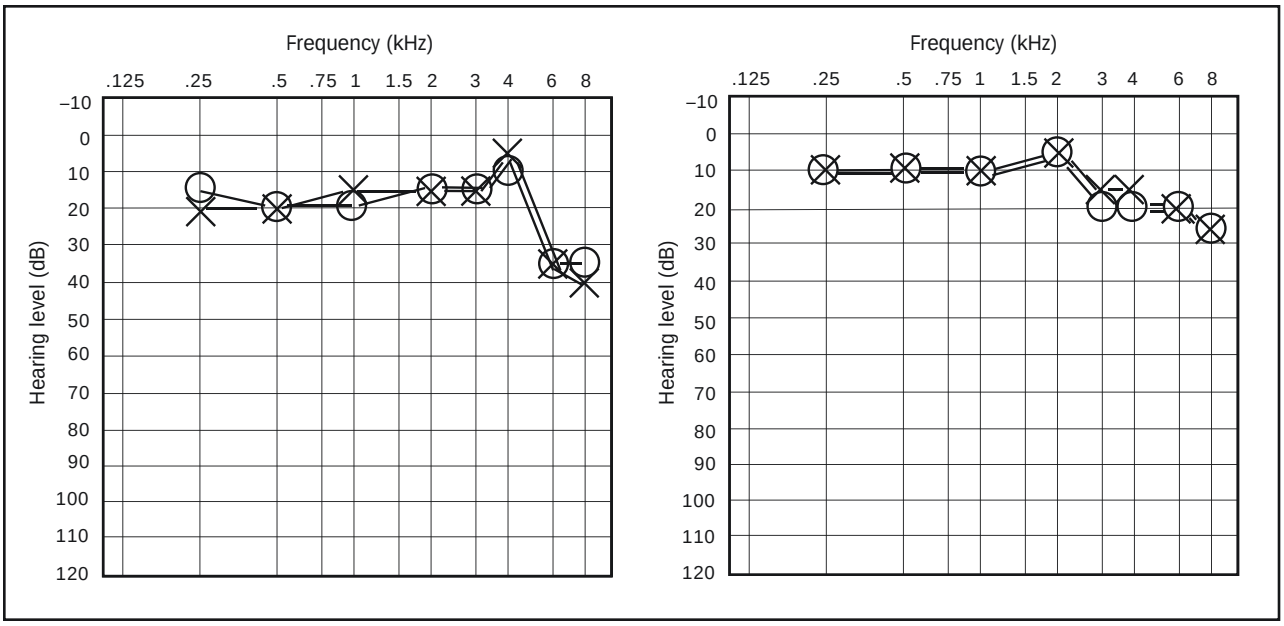

FIGURE 1. Pure-tone air-conduction hearing threshold tests (American National Standards Institute [ANSI] 1996 standards). "O" represents thresholds for the right ear and "X" thresholds for the left ear. Left, July 1999 measurement. Right, August 2002 measurement.

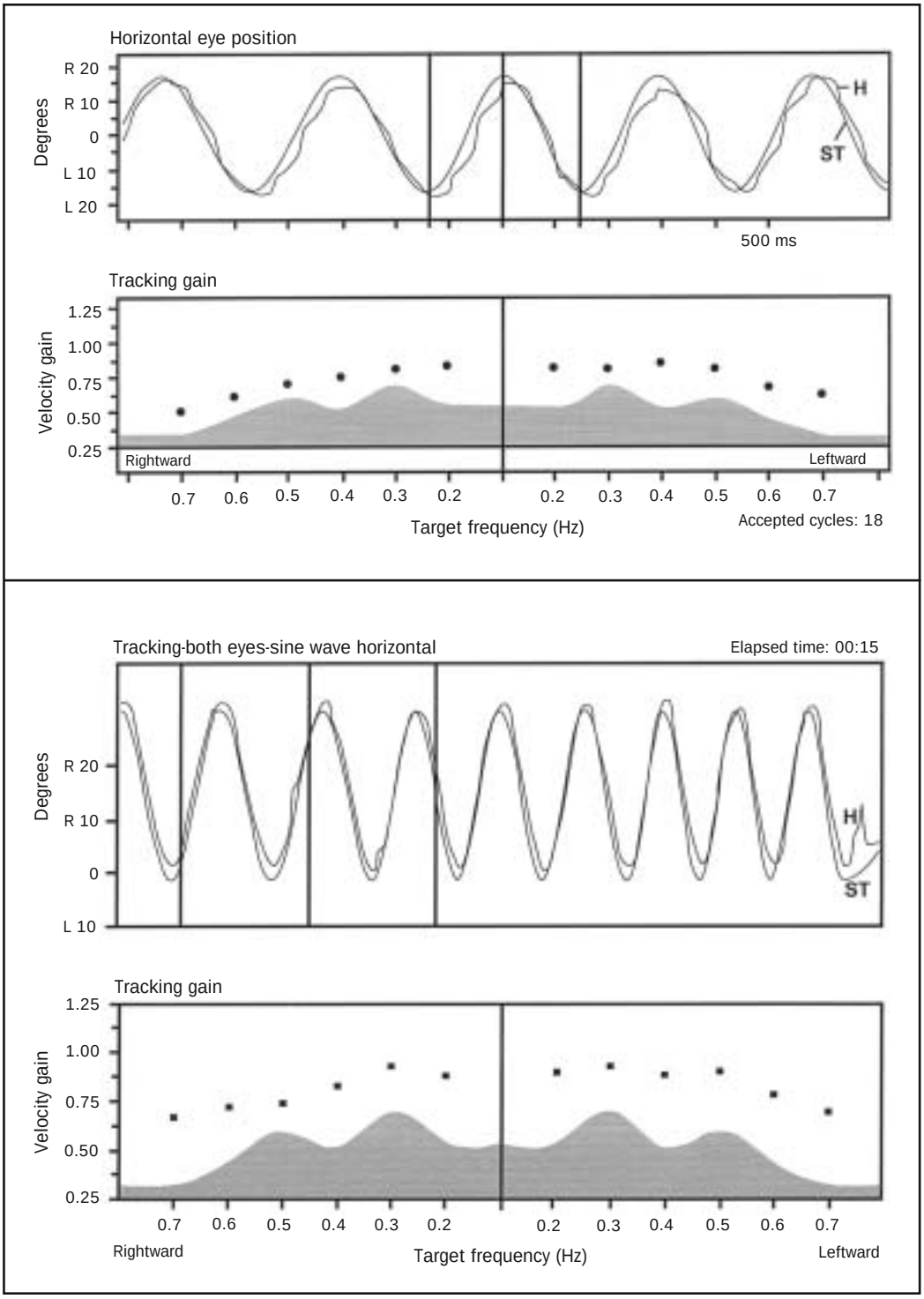

FIGURE 2. Results of smooth ocular pursuit testing. Top, Bottom panel shows mean velocity gain values measured in July 1999 (black circles) for smooth ocular pursuit from 0.2 to 0.7 Hz compared with normal values (shaded area is abnormal). Upper panel shows tracking signal for 0.71 Hz (solid smooth sine wave between the vertical lines) compared with patient's response (cogwheeling line). Right gain was 0.5, left gain was 0.66, and phase shift was –12.7°. Bottom, lower panel shows mean velocity gain values measured in August 2002 (black squares) for smooth ocular pursuit from 0.2 to 0.7 Hz compared with normal values (shaded area is abnormal). Upper panel shows tracking signal for 0.6 Hz (between the vertical lines) compared with patient's response. Note that cogwheeling seen in 1999 has resolved in 2002. Right gain was 0.65, left gain was 0.8, and phase shift was –3.2°. H = patient's horizontal pursuit; L = left; R = right; ST = stimulus.

TABLE 2. **Results of Positional Testing With Eyes Closed and Mental Alerting in Patient With Inhaled Tobramycin–Associated Vestibular Toxicity***

	Position-induced nystagmus (degrees per second)					
	Sitting	Supine	Head right	Head left	Head hanging	30° supine
July 1999	2 RB	3 RB	None	3 RB	5 RB	4 RB
August 2002	None	None	3 LB	4 RB	None	4 LB

*LB = left-beating; RB = right-beating.

Testing revealed right unilateral weakness of 9% (abnormal, >20%) and 14% right-beating directional preponderance (abnormal, >30%). Total output for the 4 irrigations was 44° per second (abnormal, <30° per second). Thus, the patient had normal, robust responses. However, even stronger responses were noted in August 2002: 33° per second in the right ear, 32° per second in the left ear, and a total of 65° per second for both ears (Figure 3, bottom).

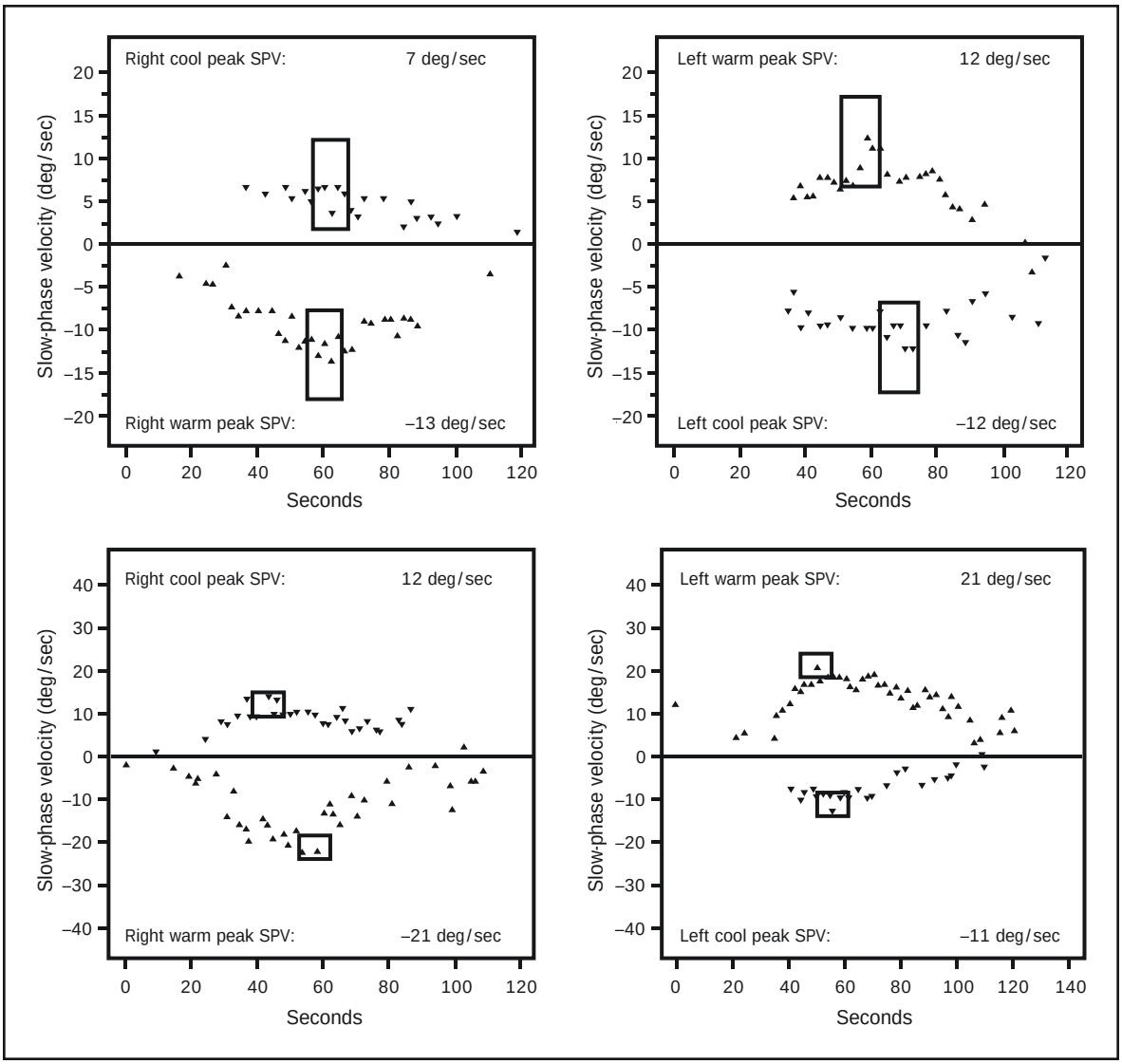

FIGURE 3. Top, Alternating bithermal binaural caloric testing in July 1999 revealed peak slow-phase velocities (SPV) of 7, –13, –12, and 12 for right cool, right warm, left cool, and left warm, respectively. Bottom, Testing in August 2002 revealed SPV of 12, –21, –11, and 21 for right cool, right warm, left cool, and left warm, respectively. (Note scale difference between top [0-20° per second] and bottom [0-40° per second].) Boxes represent a 10-second window used to calculate peak SPV. Deg/sec = degrees per second.

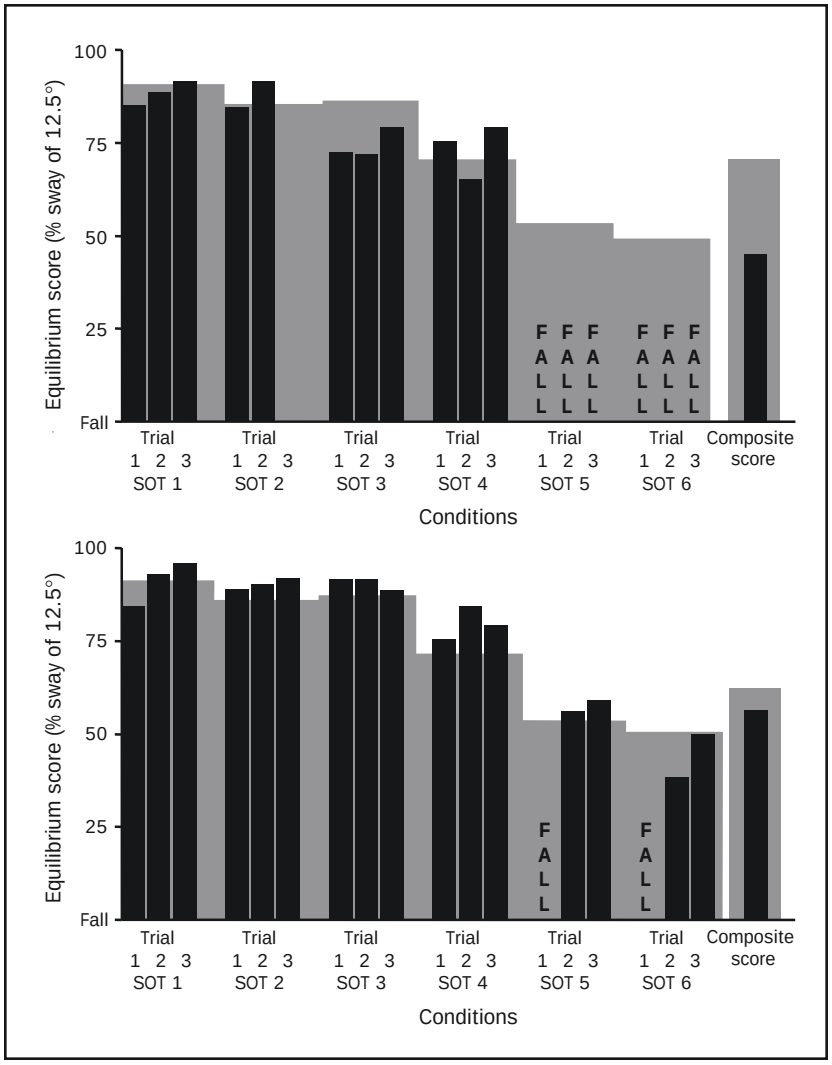

FIGURE 4. Sensory organization testing in July 1999 (top) and August 2002 (bottom). Sensory organization test (SOT) condition 1 = eyes open and wall and platform fixed; SOT 2 = eyes closed and wall and platform fixed; SOT 3 = eyes open, wall sway-referenced relative to the patient's sway, and platform fixed; SOT 4 = eyes open, wall fixed, and platform sway-referenced relative to the patient's sway; SOT 5 = eyes closed and platform sway-referenced relative to the patient's sway; SOT 6 = eyes open and wall and platform sway-referenced relative to the patient's sway. Three trials are conducted for each SOT condition. Shaded area is abnormal. The vertical text "FALL" indicates that the patient touched the wall or had to move her feet to avoid falling.

There was 2% left peripheral weakness and 2% left-beating directional preponderance. Thus, an overall increase of 21° per second (from 44° to 65° per second) occurred from 1999 to 2002.

Computerized dynamic posturographic assessment of motor control yielded normal results in both 1999 and 2002. However, findings on sensory organization testing were substantially different. In 1999, the patient had abnormal results on 7 of 11 test trials for conditions 1 through 4 (Figure 4, top). Conditions 5 and 6, which require good vestibular input, produced falls on all 6 test trials. This resulted in an abnormal composite score of 44 (70 is normal for the patient's age). In 2002, the scores had improved considerably, with abnormal results on only 1 of 12 trials for conditions 1 through 4 and only 2 falls on 6 trials for conditions 5 and 6 (Figure 4, bottom). However, the composite score was still slightly abnormal at 64.

DISCUSSION

The rationale for aerosolized delivery of aminoglycosides is achievement of high bronchial levels of drug without

TABLE 3. **Vestibular Test Data From a Patient With Inhaled Tobramycin–Associated Toxicity***

Study	July 1999	August 2002	March 2003
Dizziness Handicap Inventory	72/100 (highly abnormal)	ND	26/100 (greatly improved)
Air-conduction threshold testing	Mild loss at 6 and 8 kHz	Within reference range	ND
Oculomotor testing (smooth pursuit)	Within reference range, but cogwheeling evident at high frequencies	Normal, no cogwheeling	ND
Saccadic eye movement test	Normal velocity, accuracy, and latency	Normal velocity, accuracy, and latency	ND
Positional testing with eyes closed	Nystagmus in 5 of 6 head positions	Nystagmus in 3 of 6 head positions	ND
Caloric test	Within reference range	Within reference range, but stronger response	ND
Computerized posturography (motor control)	Normal	Normal	ND
Sensory organization test	Abnormal, with all falls on SOT conditions 5 and 6	SOT results improved dramatically	ND

*ND = not done; SOT = sensory organization test (see Figure 4 legend for definitions of conditions).

systemic toxicity. Aminoglycosides can be toxic to the hearing and balance systems.[3,4] In addition, they can be toxic to the kidneys and thereby exacerbate their deleterious effect on the inner ear. Several studies of the use of aerosolized tobramycin in humans with normal renal function have monitored serum concentrations and found them to be consistently lower than 1 mg/L and often undetectable.[5-7] Various doses were used in these studies with no ototoxicity or nephrotoxicity reported.

Although use of inhaled tobramycin has been approved for patients with cystic fibrosis and most of the reported clinical experience has been with these patients, recent reports suggest an expanding role for aerosolized aminoglycoside therapy. In a multicenter study, Barker et al[8] studied the efficacy and safety of inhaled tobramycin (300 mg twice daily via jet nebulizer for 4 weeks) in 74 adult patients with bronchiectasis who had a sputum density of *P aeruginosa* of 10^4 colony-forming units per gram. Compared with patients receiving placebo, tobramycin recipients experienced subjective clinical improvement and had significant reduction in the density of *P aeruginosa* in sputum. The median serum concentration of tobramycin was 0.54 mg/L, and no renal or eighth nerve toxicity was reported. However, adverse events affecting the respiratory tract—dyspnea, chest pain, and wheezing—were noted in many of the tobramycin recipients, and a posttreatment 4-fold increase in the tobramycin minimal inhibitory concentration was found in 26% of patients.

Sacks et al[9] recently described the use of adjunctive inhaled aminoglycosides in 19 patients with persistently smear-positive pulmonary tuberculosis. Among the patients with drug-susceptible tuberculosis who were treated with aerosolized gentamicin, sputum conversion was rapid, and no adverse effects were noted. The authors did not report serum concentrations of aminoglycosides.

To our knowledge, our patient, who was undergoing long-term hemodialysis, represents the first reported case of sustained vestibular toxicity in association with inhaled aminoglycoside therapy. Kahler et al[10] recently reported elevated trough serum concentrations (>2 mg/L) in a patient with renal failure who was receiving inhaled tobramycin; unlike our patient, this patient had no clinical evidence of ototoxicity. Inhaled tobramycin has also been associated with acute renal failure, based on a single postmarketing case report.[11]

Our patient had compromised renal excretory function that apparently enhanced the negative effect of the aminoglycoside treatment on her vestibular system (Table 3). After treatment, she had serious subjective complaints of dizziness on the basis of her Dizziness Handicap Inventory results. Three years later, her condition had improved markedly, but some vestibular deficit persisted. If the patient had been able to undergo vestibular rehabilitation (not covered by her insurance provider), even greater improvement might have been achieved. Her hearing test in 1999 showed a mild hearing loss that resolved by 2002. Objectively, she had abnormal positional nystagmus in 1999 that improved by 2002. Her caloric responses, although normal in 1999 and 2002, were stronger in 2002. Her balance, as measured on posturography after the acute attack, was grossly abnormal, but it improved markedly during the next 3 years.

Guidelines for monitoring serum concentrations in patients treated with inhaled aminoglycosides have not been published, and this route of administration can, in certain clinical circumstances, result in elevated serum levels and associated clinical toxicity. The package insert for one

preparation of tobramycin states that "caution should be exercised when prescribing [tobramycin] to patients with known or suspected renal, auditory, vestibular, or neuromuscular dysfunction. Patients receiving concomitant parenteral aminoglycoside therapy should be monitored as clinically appropriate." Further studies are needed to determine when and how frequently serum concentrations should be monitored in patients receiving inhalational tobramycin therapy, especially in patients with impaired renal function or preexisting auditory or vestibular dysfunction and in those undergoing dialysis.

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