

Update on Vestibulotoxicity: How can we Recognize and Prevent it

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Abstract: Drugs and other substances may cause irreversible damage to the inner ear. The term vestibulotoxicity refers to the toxic effect on the peripheral vestibular system and is usually caused by damage to the hair cells of the semicircular canals and otolithic organs. The devastating consequence of vestibulotoxicity is bilateral peripheral vestibular loss, including the phenomenon of oscillopsia. Parenterally administered streptomycin and gentamicin are the most common cause of vestibulotoxicity. There are few descriptions of other potentially vestibulotoxic drugs and substances, including cisplatin, solvents, organophosphate poisoning and others. Analysis of the literature shows weak evidence for true vestibulotoxicity. Unilateral vestibulotoxicity has been described after the use of ear drops containing gentamicin and, interestingly, also after parenteral use of gentamicin.

We here present an updated review of vestibulotoxicity, and suggest the appropriate investigation for suspected unilateral and bilateral vestibular loss.

Keywords: Vestibulotoxicity, Aminoglycosides, Gentamicin, bilateral vestibular loss (BVL), unilateral vestibular loss (UVL).

INTRODUCTION

Ototoxicity implies damage to the inner ear inflicted by substances, toxins or drugs. Ototoxicity can be divided into two categories: *cochleotoxic* - affecting the cochlea –the organ of hearing and *vestibulotoxic*-affecting the vesicular end organ [1]. Aminoglycosides (AGs) are a family of drugs well known for their ototoxic properties; however, their effect on hearing is much more widely recognized. In cases of vestibulotoxicity, the major damage is seen in the hair cells of the semicircular canals and otolith organs. The devastating consequence of vestibulotoxicity is bilateral peripheral vestibular loss (BVL), which significantly impairs the patient's quality of life. In order to avoid this situation, the clinician needs to know what drugs and substances may cause this effect and to recognize its clinical presentation [2].

In this review we aim to update the relevant clinical information regarding vestibulotoxicity and to demonstrate the clinical findings of both unilateral and bilateral vestibular loss.

AMINOGLYCOSIDES

Since the development of the first AGs in the 1940s, they have been used for their wide spectrum bacteriocidal action against gram negative bacteria. Currently, the family of AGs includes nine drugs approved by the FDA - streptomycin, neomycin,

tobramycin, kanamycin, paromomycin, spectinomycin, gentamicin, netilmicin, and amikacin. AGs are divided into two groups, those that were isolated from *Streptomyces* species, organic derivatives of soil-dwelling bacteria, and the synthetic AGs, such as amikacin that could be developed *in vitro*.

The major sites of adverse effects of AGs are the kidney and the inner ear. Acute tubular necrosis has been reported in 5–15% of patients after AG therapy, and requires all patients receiving these drugs to be monitored for creatinine levels. If the creatinine level rises, the drug should be discontinued and, ideally, replaced by a different drug [3]. Damage to the kidney is usually well recognized and reversible. Ototoxicity, on the other hand is often precluded by the clinical state of the patient who may be seriously ill and bedridden, making the diagnosis difficult and requiring a high level of suspicion and awareness by the physician.

The severity of ototoxicity varies among the AGs: neomycin is considered highly toxic; gentamicin, kanamycin, and tobramycin somewhat less; and amikacin and netilmicin are regarded as the least toxic. As far as the affected part of the inner ear, gentamicin and streptomycin are predominantly vestibulotoxic, whereas the rest of the AGs are mainly cochleotoxic. In addition delayed effect of kanamycin was clearly evident in the vestibular system.

Although the adverse effects of the drugs are well known, administering AGs continues, especially in the developing world, due to their low cost and high efficacy against infections of gram negative bacteria.

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Vestibulotoxicity occurs in up to 15% of patients after AG administration, whereas cochleotoxicity occurs in 2% to 25% of patients [4-6].

The Mechanism of Damage

In parenteral administration of AGs the damage is due to hair cell toxicity [5]. The complete mechanism is not known but there are several hypotheses:

1. In vestibulotoxicity, AGs cause loss of type 1 and type 2 hair cells. Another effect of AG is the toxicity of the stria vascularis and a decrease in the number of marginal cells [6].
2. Reactive oxygen (ROS) (free radicals): AGs are not toxic themselves but when they chelate to a metal ion like iron they give rise to reactive oxygen (ROS), free radicals and reactive nitrogen species (RNS) and thereby have the capability of mutilating nearby biomolecules. The generated toxic agents not only cause molecular damage but also initiate cell death *via* apoptosis and necrosis [7].

Streptomycin

The initial isolation of streptomycin from *Streptomyces griseus* provided the long-sought treatment for tuberculosis and an effective antibiotic against gram-negative bacteria. The nephrotoxicity and ototoxicity were initially discovered in the first clinical trials of streptomycin, shortly after its discovery. The first report was by Walsh in 1947, who demonstrated that onset of vestibular dysfunction appears to bear a definite relationship to triple daily dose and the duration of treatment. Affected patients complained of headache or a sensation of "heaviness in the head", which disappeared within twenty-four hours and was followed by the development of a sensation which resembles vertigo. The symptom differed from true vertigo, lacking a rotary component [8]. Overall, ototoxicity has been estimated to occur in 5-30% of patients treated. Modification of streptomycin to dihydrostreptomycin, however, resulted in a shift of ototoxic damage from the vestibular organ to the cochlea [9].

Data in the human about the oto-pathology of streptomycin are sparse. Nadol [10] found loss of hair cells in the cristae in two individuals who developed ataxia after administration of streptomycin.

Tsuji *et al.* [11] performed quantitative assessments of the vestibular end-organs in eight bones from four

individuals with clinically documented vestibulotoxicity from streptomycin; they found a significant loss of type I and type II hair cells in all five vestibular sense organs. Further, there was greater loss of type I hair cells (as compared to type II hair cells) for all three cristae but not for the maculae.

Ishiyama *et al.* [12] found a significant loss of Scarpa's ganglion cells in three specimens with a clinical history of streptomycin vestibulotoxicity. There was also loss of hair cells in the utricular macula and the lateral canal crista.

Gentamicin

Gentamicin was developed in the 1960' and is the main cause of drug vestibulotoxicity, classically causing BVL.

Recently, Ahmed *et al.* [13] described a case series of 103 patients with vestibulotoxicity, following gentamicin therapy, over a 23 year period. This complication was observed among 21 patients during the treatment period, in 66 following treatment, while 16 patients could not recall exactly when symptoms initiated. Three of the patients had noted some hearing impairment after receiving gentamicin, but audiometric thresholds for all patients were found consistent with their age. The authors concluded that gentamicin ototoxicity is completely vestibular and not cochlear, producing permanent loss of balance. Black *et al.* [14] analyzed retrospective and prospective studies of a total of 33 subjects with permanent gentamicin-induced vestibulotoxicity. They showed that regardless of serum gentamicin peak and trough levels, vestibulotoxicity could not be avoided. They could not recommend a "safe dosage range" to prevent the permanent gentamicin-induced vestibulotoxicity. Regarding the oto-pathology of gentamicin Bagger- Sjöbäck *et al.* [15] examined temporal bones of two cases that had been treated with gentamicin but had not responded, leading to labyrinthectomies. In both cases, vestibular tissue remained, but the organ of Corti was totally absent, suggesting that the treatment may have had more drastic effects on the cochlea.

The issue of the effect of gentamicin on premature infants and children was examined in certain studies. Two studies prove that gentamicin in controlled therapeutic doses has a significantly lower cochleotoxic and vestibulotoxic effect in newborns than reported in older children and in adults [16, 17]. In contrast Eviatar and Eviatar [18] searched for abnormalities in

neurovestibular responses in 43 infants who had been treated with aminoglycosides during the neonatal period. The results were compared with those obtained from a group of 276 untreated healthy newborns. No abnormalities were found in the untreated group. Among the treated infants, three had sensorineural hearing loss and eight had laboratory evidence of vestibular dysfunction and delay of head and postural control. Positional nystagmus was found in 6 of 26 infants treated with kanamycin and in 10 of 17 infants treated with gentamicin. Other findings included directional preponderance and diminution of caloric response. The authors recommended that infants undergoing aminoglycoside therapy should be monitored with auditory and vestibular tests and at the first sign of abnormality, a careful assessment should be made as to whether continuing treatment is prudent.

Ahmed *et al.* [19] reviewed 18 adult patients presenting with imbalance and oscillopsia after parenteral admission of gentamicin, who developed unilateral vestibulotoxicity. In the acute period their symptoms were exactly the same as those of patients with BVL. Only 4 of the 18 patients reported previous gentamicin therapy, while in the rest, the previous use of gentamicin was only discovered through chart reviews. They concluded that patients receiving vestibulotoxic agents should be urged to report on oscillopsia and imbalance rather than vertigo, tinnitus and hearing loss.

TOPICAL PREPARATIONS AND OTOTOXICITY

Suppurative chronic otitis media and acute otitis media are commonly treated with topical antibiotic ear drops. Ear drops easily enter the middle ear space through the perforated tympanic membrane or *via* pressure equalizing tubes (ventilating tubes). Some of these ear drops have contained gentamicin [20]. This local effect of gentamicin published in treatment of intractable Ménière's syndrome with intratympanic administration of aminoglycosides has become common because of the high rate of success in eliminating vestibular distress. One cost of this success is that hearing loss can also occur [21]. The risk of additional hearing loss after gentamicin treatment is about 20% [22]. A similar rate of hearing loss was reported for streptomycin treatment [23].

However, it had been thought that infection of the mucosa of the middle ear would serve as a barrier for penetration of the drops into the inner ear and many clinicians prescribed them, unaware of their potential toxicity [24].

The majority of studies regarding AGs containing ear drops review the damage to the cochlear, reflected by hearing loss. One study found the incidence of ototoxicity as 1:10,000 or lower [25]. Bath *et al.* [26] had published a retrospective case series of 16 patients with vestibulotoxicity caused by gentamicin containing ear drops (Garasone®- 1 mL contains 3.0 mg gentamicin sulfate and 1.0 mg betamethasone sodium phosphate). All subjects had a tympanic membrane defect, and used topical gentamicin-containing eardrops for longer than 7 days before the symptoms of vestibular damage had appeared. The symptoms ranged from acute vertigo to imbalance and oscillopsia, and the effect was confirmed on electronystagmography (ENG) testing. Several years later, following this publication, Garasone® was banned in Canada for ears with perforations.

In 2004 the American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) updated their recommendations, as follows [27]:

1. When possible, topical antibiotic preparations free of potential ototoxicity should be preferred over ototoxic agents that have the potential for ototoxic injury, if the middle ear and mastoid are exposed.
2. If potentially ototoxic antibiotics are prescribed, the patient should be specifically instructed to call the physician or return to his or her office, if the patient develops the following: dizziness or vertigo, hearing loss, or tinnitus.
3. If the tympanic membrane is intact and the middle ear and mastoid unexposed, then the use of potentially ototoxic preparations presents no risk of ototoxic injury [28].

During the recent decade alternatives to AG drops, particularly quinolone drops are readily available. The quinolones are superior to the AGs in terms of safety, bacterial eradication, and clinical cure and are therefore the drops of choice for treating otorrhea in an open- infected ear [29].

OTHER DRUGS AND SOLVENTS WITH POSSIBLE VESTIBULOTOXIC EFFECTS:

Cisplatin

Cisplatin was synthesized in 1845 by Peyrone and in 1965 Rosenberg discovered the ability of the platinum compounds to inhibit cell division [30]. In 1987

Kobayashi *et al.* [31] reported association between cisplatin and cochlear and vestibular toxicity. The symptoms appeared to be almost all transient and occurred after several weeks of administration. On physical examination abnormal findings such as spontaneous nystagmus and positional nystagmus were seen. Caloric tests and body sway tests detected abnormal findings in the early stages of cisplatin-related vestibulotoxicity. But in later reports it seemed that cisplatin has a much lower likelihood to cause vestibulotoxicity and is mostly associated with a higher occurrence of hearing deficits [6].

Antiseptics (Chlorhexidine, Cetrimide and Savlon)

Chlorhexidine and/or cetrimide are used to clean wounds and to prevent infection during surgery. Vestibular dysfunction has been demonstrated after chlorhexidine or cetrimide had been used to rinse the external auditory canal with tympanic membrane perforation in cats, dogs and in guinea pigs [32]. The vestibular dysfunction has been observed immediately after awakening from anesthesia. In addition, light microscopy revealed loss of sensory epithelium and fibrosis of the cochlea. With use of higher antiseptic concentrations the morphological changes appeared earlier. In humans, Bicknell [33] reported the first evidence of potential damage from these materials, using 0.5% chlorhexidine with 70% ethanol, leading to cochleotoxicity with no referral to vestibulotoxicity.

Savlon® is a solution of 1.5% chlorhexidine gluconate and 15% cetrimide in distilled water, not found to cause vestibular adverse effects.

Organophosphate (Anticholinesterases)

Very limited data exists on possible vestibulotoxicity of organophosphates. A cohort cross-sectional study [34] was conducted on 18 rural workers who were exposed to organophosphate. All workers went through otorhinolaryngological, audiological, and a vestibular examination. Sixteen of the patients (88.8%) showed a bilateral hyper-reflexia on calorics, suggestive of cerebellar disorders, as a part, a slow, and a silent intoxication. Interestingly 7 workers had sensorineural hearing loss.

An early study in the German language [35] followed patients (no number is mentioned) after organophosphate poisoning. All patients suffered temporary balance disturbance that resolved after 4 months. The authors also claim positional nystagmus with no mention of vestibular testing results.

Organic Solvents

Solvents used in industry that are mostly known to affect hearing have synergistic effect when combined with noise exposure. These materials include toluene, styrene, carbon disulfide, trichloroethylene and xylene. Hodgkinson *et al.* [36] reviewed research from the last four decades on industrial solvents and their adverse effect on the auditory and vestibular systems in both animal and human experiments. Solvents typically cause toxic encephalopathy with clinical signs and vestibular testing results in keeping with central and not peripheral vestibular deficits [37, 38]. From analyzing these publications it seems clear that they do not represent vestibulotoxicity.

Lidocaine

Shemirani *et al.* [39] reported a case study of a 76 year old patient suspected of developing vestibulotoxicity following the use of a transdermal lidocaine patch and heating pad on his lower back for about 14 hours. They report on a continuous sensation of imbalance preventing him from ambulating and intense vertigo with each movement. He felt as though his "entire balance system had failed". After recovery, there was a subjective improvement in hearing acuity and resolution of his long-standing tinnitus. He denied headache, otalgia, otorrhea, or aural fullness. The patient experienced acute and severe disequilibrium persisting for 48 hours but no neurotological and vestibular testing was performed to confirm a clear vestibulotoxic effect.

Phosphodiesterase Inhibitors (Cialis, Viagra, Revatio and Levitra)

Maddox *et al.* [40] reported two cases and reviewed FDA post-marketing data regarding PDE5 (phosphodiesterase type 5 inhibitor) and sudden sensorineural hearing loss (SSHL). Vestibular affects have not been reported. Still, they note that some phosphodiesterase inhibitors (such as Cialis, Viagra, Revatio, and Levitra) require safety warning because administration may be associated with sudden hearing loss and, possibly, vestibular disturbances.

Organometals (Organic, Mercury)

Oyanagi *et al.* [41] reported a neuro-pathological investigation on 14 autopsy cases of methyl mercury intoxication and 12 age-matched controls. The neuro-pathological results were compared to the records of the equilibrium function of those patients. The

disequilibrium in the patients of methyl mercury intoxication did not correspond to the degeneration of the vestibular ganglion, nerve or nuclei. In conclusion, the study did not confirm vestibulotoxicity by mercury.

CLINICAL ASPECTS OF VESTIBULOTOXICITY

The clinical presentation of vestibulotoxicity depends on whether the effect is unilateral or bilateral and, by the magnitude of injury, mild to severe. A brief review of the main characteristics of unilateral and bilateral vestibular loss will be described. For a more in-depth description on the neurotological examination and on vestibular tests of the vestibular system the reader is advised to refer to the following reference [42].

As with any patients complaining of vertigo, gait or balance disorders, a complete history is the hallmark of diagnosis. The patient should be questioned on the onset, duration and severity of the handicap, and past and present use of medication, including the use of ear drops. Testimony of family members may prove essential in gathering the exact sequence of events leading to the patient's complaints. Hospital and ambulatory medical records should supply the clinician with information regarding the time of medication, serum levels of the drugs, duration of treatment and whether any symptoms of ototoxicity were present. Seldom will the patient directly volunteer a history of receiving parenteral AGs; however, the recent history will usually reveal a lengthy hospitalization during which he or she had received AGs. The patient should also be questioned regarding symptoms of cochleotoxicity- a recent onset of hearing loss or tinnitus.

BILATERAL VESTIBULAR LOSS (BVL)

BVL causes gait disturbances and imbalance and is usually manifested without true vertigo, as both inner ears are affected simultaneously. These patients are at high risk of falling and they commonly experience severe handicap in everyday activities, some patients being handicapped to the degree that they become bedridden. The patient may also complain of *oscillopsia*- the inability to see clearly while moving his or her head. This symptom is caused by the loss of the vestibular input to the occulo-motor muscles, bilaterally.

The difficulty in diagnosing BVL following vestibulotoxicity lies in the fact that bedbound patients may not be aware of their imbalance until they return to walking. Classically, in the scenario of treatment with gentamicin, unawareness of the physician to the

possible cause of the imbalance may cause continuation of treatment, so that damage increases and becomes irreversible.

A complete otoneurological examination should be performed including otoscopy, examination of the cranial nerves, occulo-motor tests, cerebellar function, gait and positioning.

A clinical diagnosis of BVL can be made at the bedside by performing the *head impulse test (HIT)*, described by Halmaghyi *et al.* [43]. The patient is asked to fixate on the examiner's nose, while, the examiner rotates the patient's head quickly to the left or right, observing the eye movements. In a normal subject the eyes will move contralaterally, to the head movement- signifying a normal vestibulo-ocular response. In a patient with BVL the eyes will move with the head, so that the patient will have to make catch-up saccades after the head movements to bring the eyes back on target. In cases of both unilateral and bilateral vestibular loss evidence of the catch-up saccades indicates the affected side – one or both. A positive HIT bilaterally, suggests BVL.

Dynamic Visual Acuity (Testing for Oscillopsia)

The examiner oscillates the patient's head from side to side in the horizontal plane. The patient is asked to read the letters or numbers on the Snellen chart, while the head is moving. A patient with bilateral vestibular loss will, typically, lose three or more lines compared to static visual acuity [44].

In an ambulant patient it is useful to examine the *Romberg test*, preferably performing it on rubber-foam mattress, making the exam more sensitive. The patient is asked to place feet together and close the eyes. Given normal proprioceptive function, a patient with total BVL will fall off the mat. The examiner must be ready to prevent the fall [45].

A patient with BVL will use a wide gait and will not be able to perform the *tandem gait exam* properly, even with eyes open. The audiometry will usually be unaffected, unless there is cochlear damage, too (cochleotoxicity).

Oculomotor and cerebellar tests are expected to be normal, helping to distinguish the cause of imbalance from central etiologies. Positioning examinations, aimed at diagnosing benign paroxysmal positional vertigo (BPPV) are also expected to be normal.

The clinical signs of BLV should be confirmed on vestibular testing. The bithermal caloric videonystagmography (VNG) or electronystagmography (ENG) will show decreased values of slow phase peak nystagmus, totaling less than 20 degrees per second.

Other vestibular testing such as computerized dynamic posturography (CDP), and rotatory chair may also be useful but are usually less available. Zingler *et al.* [46] reported that roughly 80% of patients with BVL do not improve.

UNILATERAL VESTIBULAR LOSS (UVL)

In contrast to patients with BVL, most patients with UVL will recover within a few weeks and become asymptomatic and around 20% will develop chronic vestibular insufficiency [47, 48]. As in other etiologies of UVL, the main symptoms are vertigo, nausea and vomiting; however during the acute stage UVL may share certain features with BVL, such as imbalance, ataxia and even temporally oscillopsia.

The otoneurological exam may show spontaneous nystagmus, but this finding is usually inhibited by central compensation mechanisms, within several days. In the acute phase an abnormal Romberg exam, a wide gait and failure to perform tandem gait, even with eyes open resemble findings of a patient with BVL. The HIT would be expected to be positive on the affected side, only. There may also be *post head shake nystagmus*, caused by asymmetry in the velocity storage mechanism between the two sides. This test is performed by gently shaking the head of the sitting patient, for 20 seconds, and afterwards examining for nystagmus. Several beats of horizontal nystagmus, with the fast phase directioned contra-lateral to the affected ear is the typical finding [49]. As in BVL, oculomotor exams, cerebellar exams and positional testing are expected to be normal.

Bithermal caloric ENG/VNG will confirm unilateral vestibular loss, demonstrating a significant reduction of values of slow phase - peak velocity nystagmus in the affected compared to the unaffected side; excitability difference. Usually a 25% or more reduction in the affected side is considered diagnostic.

Unfortunately, BVL is usually irreversible and does not respond significantly to physical therapy. Graded physical activity may aid in balance function [50]. In contrast, UVL even if it becomes permanent, usually undergoes central compensation and patients recover well.

SUMMARY

Our literature search found that vestibulotoxicity is mostly limited to AMs, with low evidence for other drugs causing this effect. Although vestibulotoxicity is a rare phenomenon, it is a proper risk when administering gentamicin, parenterally and in ear drops. This may cause irreversible bilateral peripheral vestibular loss with devastating consequences for quality of life. Unfortunately, vestibulotoxicity is seen even when gentamicin levels are normal, so prevention of this complication is based on limiting use of the drug and on close clinical follow-up.

It is also important to recognize that gentamicin containing ear drops as well as solvents may cause a direct toxic effect on the ipsilateral labyrinth, which may also cause a substantial handicap. Understanding this potential risk and being able to recognize symptoms and signs of vestibulotoxicity, is therefore, important.

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