

Aminoglycoside-induced balance deficits: a review of vestibulotoxicity

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Abstract

This article aims to inform clinicians about the current knowledge on aminoglycoside-induced vestibulotoxicity through a review of the literature. The effects of vestibulotoxicity are irreversible and may be profoundly disabling. It would appear that the sooner vestibular rehabilitation therapy is instituted, the more favourable the prognosis is. Thus, early referral and management are essential. Vestibulotoxicity is a commonly overlooked aetiology when assessing dizzy patients. This could be due to the difficulty that patients have in describing vestibular symptoms in general, as well as the absence of vertigo as a presenting complaint. Discussion includes the clinical presentation of vestibulotoxicity and its sequelae, as well as strategies to assess and monitor patients.

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Introduction

A variety of drugs and topical agents may cause vestibulocochlear toxicity, commonly referred to as ototoxicity.¹ One of the classes of medication known for its ototoxic potential is the aminoglycosides, which can damage either the hearing or the vestibular apparatus or both. Vestibulotoxicity is the ability of a substance to destroy or damage vestibular structures, which could involve the end-organ at hair cell level, the vestibular aspect of the eighth cranial nerve and connections within the central nervous system.² Aminoglycosides are effective against serious enterococcal and Gram-negative infections, low in cost and easily accessible, factors that are important when clinicians are making choices about medication.³ Thus, the clinical problem of adverse outcomes in response to medication, in this instance vestibulotoxicity, is an ongoing issue that has major relevance for all practitioners who care for patients receiving aminoglycosides.

Aminoglycosides have the ability to target different areas of the cochleovestibular system selectively. Of critical importance is the fact that vestibulotoxicity can exist independently from cochleotoxicity. Gentamicin is the most commonly used drug that is administered in a form (i.e. parenterally) and dosage that may cause damage, usually vestibulotoxicity.^{4,5} Of particular concern is the widespread use of gentamicin in neonates at risk of sepsis, many of whom may be premature and have suboptimal renal function.⁶ A small study performed recently suggested that damage to the vestibular apparatus does occur in infants after as few as three doses of amikacin.⁷ Other

aminoglycosides such as streptomycin and kanamycin are used predominantly in the treatment of tuberculosis.⁸⁻¹⁰ Streptomycin has been found to be primarily vestibulotoxic and has a fairly minor cochleotoxic effect.¹¹ It is reasonable to assume that in spite of their toxicity, aminoglycosides will be used far into the future, as the incidence of tuberculosis and multidrug-resistant tuberculosis has been severely aggravated by the human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) pandemic.¹²⁻¹⁵

The major symptoms of vestibulotoxicity are dizziness, dysequilibrium and oscillopsia, as distinct from vertigo, which would be a most unusual presentation. The effect of vestibulotoxicity is permanent and may affect an individual's quality of life negatively. The development of vestibulotoxicity may prolong hospitalisation, necessitate intensive vestibular rehabilitation therapy and jeopardise the patient's income, should he or she be unable to drive or hold down a job.¹⁶ The next section of this review further explores the disabling nature of dizziness.

Disability and quality of life

Dizziness has been shown to cause difficulties in many of the activities of daily living, and to impact profoundly on the sufferer's quality of life.¹⁷ Impairments that may result from disorders of the vestibular system include gaze instability, altered perception of motion and orientation in space and the inappropriate use of balance strategies, which develop during the compensatory stage.¹⁸ Specifically, issues that may result from bilateral vestibular hypofunction, often as the result of vestibulotoxicity, include oscillopsia, gait

ataxia, nausea, light-headedness, veering when walking and an increased risk of falling.¹⁹ Because of these symptoms, patients should be advised to avoid heights, operating machinery and driving until they are assessed as able to do so with safety.²⁰ For vestibulotoxic patients with a guarded prognosis for recovery, the ramifications of these restrictions would obviously depend on the patient's occupation. However, the magnitude of disability caused by vestibulotoxicity should not be underestimated. In one study, all of 33 participants were disabled after gentamicin vestibulotoxicity.²¹ None of the individuals resumed their premorbid occupations, and 32 became dependent on disability and social grants.

In addition to the physical limitations imposed on vestibulotoxic patients, there are other effects. Magnetic resonance imaging evidence has suggested that the hippocampus may atrophy in cases of bilateral vestibular hypofunction, and that this could be linked to a range of cognitive deficits. Vestibular damage in the hippocampus could also be the cause of emotional changes that result in anxiety and depression.²² Psychological distress and disability in participants with vertigo (including vestibulotoxicity) is greater than expected, with anxiety and depressed affect.²³ Another study highlighted that the most troubling handicaps of vestibular hypofunction were social and physical restrictions of activities, worry and a lack of confidence.¹⁷ Importantly, these feelings of not being able to cope may lead to activity restriction, which in turn reduces the chance of any recovery. Considering the permanent damage that occurs in vestibulotoxicity, also noteworthy was the link between the length of time that patients had lived with their illness and the levels of somatic anxiety, disease-specific handicap and decreased psycho-social functioning.¹⁷ While vestibulotoxicity was not addressed specifically, it can be argued that the limited response to therapy and the permanent nature of vestibulotoxicity would cause even more profound disability. Hence, vestibulotoxicity triggers a combination of physical and psychological symptoms that result in a deterioration in the quality of life, and even in the earning potential.

Factors influencing occurrence

Differences in study design and methodologies have resulted in variable and controversial data regarding the incidence of vestibulotoxicity.^{8,24,25} Many of the reports have small numbers of participants and thus lack generalisability. Risk factors for the development of vestibulotoxicity may be broadly summarised under three main considerations: drug variables, patient variables and the awareness of the attending clinician.²⁶

Drug variables

Early research suggested that 3–5% of patients treated with streptomycin would become vestibulotoxic, while later research suggested that this figure could be as high as

10%.^{27,28} Gentamicin was found to be vestibulotoxic in two-thirds of patients who received it.²⁹

Apart from the choice of drug, additional factors that may influence vestibulotoxicity are dosage issues, in terms of quantity and frequency, and duration of treatment. Commonly employed treatment protocols for tuberculosis suggest that dosages of aminoglycosides may be calculated according to categories of body mass (e.g. 50–75 kg).¹⁵ Animal studies have suggested that ototoxicity was more marked when the animals were nutritionally deprived.³⁰ Thus, it is possible that patients at the lower range of such a broad weight band would be at higher risk. Some authors recommend a once-a-day dosage rather than splitting the dosage into two per day,³¹ however, only a few studies with a limited number of participants have examined the link between once-daily administration and vestibulotoxicity.¹⁶ Whilst it would be obvious that continuous exposure would increase the risk, it should be noted that aminoglycosides can be vestibulotoxic within short treatment periods.⁷

Patient variables

In the diagnosis of the majority of vestibular disorders, it is generally agreed that the quality of history taking is of critical importance. It would seem obvious to ask patients about the onset or aggravation of symptoms such as hearing loss, tinnitus, nausea or dysequilibrium. However, symptom description cannot reliably be used to identify or track vestibulotoxicity for a variety of reasons.³² First, patients with severe vestibulotoxicity suffer from slowly progressive bilateral vestibular hypofunction and so the presenting complaint is most unlikely to be acute, severe vertigo.³² Perpetual dizziness, dysequilibrium, ataxia and oscillopsia, rather than vertigo, are the typical presentation of vestibulotoxicity.^{16,32,33} These symptoms are only apparent when patients are mobilised and are often incorrectly attributed to the patient's debilitated state.^{33,34} Second, patients may use various terms for the symptom of dizziness, ranging from "weak" and "sick", to "giddy" and "spinning".³⁵ Some of these words may not alert staff to the possibility of vestibular dysfunction. Third, in a multilingual setting such as South Africa, there may not be words in indigenous languages to describe the symptoms of vestibulotoxicity adequately. Attending staff with linguistic backgrounds that differ from those of their patients may easily misinterpret nebulous symptom reports that would otherwise alert them to vestibulotoxicity.

Risk factors for cochleotoxicity include genetic susceptibility, renal impairment, hyperthermia, dosage in relation to weight, concomitant treatment with other oto- or nephrotoxic medication, prior or prolonged exposure to ototoxic medication, pre-existing dysfunction, advanced age and poor nutrition.^{26,36} However, there are little data to support these suppositions when applied to vestibulotoxicity.¹⁶

Healthcare practitioner variables

In the moribund patient the primary consideration is, understandably, saving the individual's life. Thus, the use of aminoglycosides could be argued to justify the risk of adverse drug effects, and this will heavily influence decision making. In cases where aminoglycosides are given, the clinician's knowledge concerning vestibulotoxicity will have an impact on the accuracy and speed of diagnosis and the prognosis.²⁶ As the symptoms of dysequilibrium and oscillopsia may not be obvious, especially if the patient is bedridden, they may be overlooked. One study suggested that most patients with permanent gentamicin vestibulotoxicity were not diagnosed prior to discharge from hospital.²¹ Patients complained of symptoms only to have them ignored or incorrectly treated, suggesting that doctors' knowledge of vestibulotoxicity is not adequate.³³ It would be extremely unusual for patients with vestibulotoxicity to display the sign of nystagmus or symptoms of vertigo.²⁶ Thus, it is disappointing to note that in publications such as the World Health Organization's Treatment of Tuberculosis Guidelines for National Programmes,¹⁵ nystagmus and vertigo are listed under adverse drug effects for aminoglycosides; events that are most unlikely to occur given the mechanism of bilateral vestibular failure. This in turn could lead to missed diagnoses among practitioners expecting to see these signs.

Clinicians may be unaware that vestibulotoxicity can occur without cochlear hearing loss.³⁷ There is no correlation between serum or plasma levels and vestibulotoxicity; vestibulotoxicity may still occur in spite of measured "non-toxic" levels of the drugs.^{10,21,36} Both these examples demonstrate how the knowledge of the clinician may impact on patient management.

In addition to awareness of vestibulotoxicity, the attitude of the staff attending to patients undergoing treatment with aminoglycosides may have an impact on the likelihood of symptoms being reported, and even on a decision to investigate these symptoms. Research into attitudes of nurses in South Africa caring for patients with tuberculosis suggested that nurses could be authoritarian, scolding and frustrated.³⁸ This could result in the patients' unwillingness to raise complaints.

Diagnosis

The effect of ototoxic drugs on vestibular function is not always clear.³⁹ Several issues compound the diagnosis of vestibulotoxicity. Methods available to evaluate vestibulotoxicity are not always sensitive enough to demonstrate the subtle changes that could uphold the diagnostic symptoms.³⁹ For example, it was postulated that a reduction of 20–40% in hair cells may be necessary before canal paresis will be evident on caloric testing.⁴⁰ In addition, behavioural and reflex tests are frequently unable

to differentiate between peripheral and central vestibular damage,³⁹ making precise site-of-lesion diagnosis difficult, which could in turn affect vestibular rehabilitation therapy decisions. Finally, vestibular assessment is extremely challenging in ill patients.⁸

Testing options range from bedside examinations to sophisticated specialised testing. Both can be used for either diagnostic or monitoring purposes.

Bedside examination

Bedside testing can yield important diagnostic information. The expected results of bedside tests that would be associated with vestibulotoxicity are shown in Table I.

Special investigations of vestibular function

Tests that utilise specialised equipment can quantify vestibular function, but are not diagnostic in themselves.⁴² While the literature offers reports of the sensitivity and specificity of various tests of vestibular function, which are summarised in Table II, it should be stressed that these tests are time consuming and difficult to administer to patients who are acutely ill or moribund. Furthermore, a battery of tests, all dependent on different and expensive pieces of equipment, may be required to build an overall picture of a patient's balance and postural control. Finally, the equipment is usually only found in specialised facilities and the personnel required generally have to be specially trained, experienced and competent individuals.

Treatment

Spontaneous recovery from vestibulotoxicity

Reports concerning the level of recovery of vestibular function in cases of bilateral vestibular hypofunction are sparse and reflect contradictory results. It was noted that regeneration of receptor cells damaged by gentamicin was possible.⁴⁹ However, in a study by the same authors, which examined functional recovery of balance, there was no improvement in a large majority (80%) of chronic cases of vestibulotoxicity. It should also be noted that vestibulotoxicity may continue to progress, even once the drug has been withdrawn.^{21,32}

Pharmacology

The use of medication in treating dizziness and vertigo is challenging and does not always yield optimal results.⁵⁰ A balance must be struck between symptom control and undesired side-effects, such as sedation and delay in or prevention of compensatory processes.⁵¹ In general, drugs that are known to reduce the symptoms of certain forms of otological vertigo (such as vestibular suppressants) have been described as aggravating the symptoms of bilateral vestibular hypofunction.⁵⁰ Because of the issues concerning the quality of life of those who have vestibulotoxic hypofunction, some level of depression could be expected.

Table I: Bedside tests of vestibular function, and results if the patient has bilateral vestibular hypofunction (adapted from Black and Pesznecker⁴¹)

Test	Aim of evaluation	Results if vestibulotoxic	Notes
Inspection for nystagmus	Establish presence and grade of spontaneous and/or gaze nystagmus.	No nystagmus will be evident as loss of ^a VOR input is usually symmetrical.	Requires experienced clinician. Reliability enhanced if Frenzel lenses are used.
Head thrust test	Establish if VOR input is present and normal.	Will have saccades in both directions.	Need appropriate training. Should be a routine test. Sensitivity of 84–100% if bilateral vestibular hypofunction.
Dynamic visual acuity test	Establish if patient has early oscillopsia.	Will have decline in vision when head is moving.	Snellen chart or similar required. Should be a routine test.
Standard Romberg	Tests vestibulospinal reflexes.	Positive with falls when acute.	May become negative if loss is compensated for.
Sharpened Romberg (tandem position)	Attempts to be more of a test of vestibular function by reduction of proprioceptive cues.	Cannot assume position when acute.	May be possible with eyes open if compensated, not with eyes closed.
Gait	Identify ataxia and gait abnormalities.	Wide based, slow, may need assistance when acute.	Even when compensated may have a shortened step length.
Falls and fall risk		Patient at great risk of falling.	Remains greater in all age groups even when compensated. May need assistive device or may result in decreased activities.
Bedside caloric test	Establish function of lateral semicircular canal.	Reduced response bilaterally.	Reliability enhanced if clinician is experienced. Better results obtained if headlight and Frenzel lenses are used. Patients with no or reduced response should be referred for formal testing. Crude test, does not test whole system.

a= Vestibulo-ocular reflex

Table II: Sensitivity and specificity of laboratory investigations to establish the presence of peripheral vestibulopathy. All tests can be performed over time and thus there is a potential for monitoring.

Test	Aim of evaluation	Advantages	Disadvantages	Sensitivity	Specificity
^a ENG ⁴²⁻⁴⁶	Examines ^b VOR, additional information on oculo-motility.	Widely used, established technique. Evaluates in eyes-closed condition, which is preferable for peripheral vestibular nystagmus. Calorics: evaluates each ear separately. Reasonable consensus as to what is abnormal. Reflects permanent deficits.	Lack of standardised norms, especially in elderly populations. Calorics: very slow stimulus; wide variability in strength of stimulus; only lateral semicircular canal tested. Does not reflect dynamic compensation.	31% 29–56%	86% Limited
^c ROTO ^{42,45-48}	As above	Very useful to establish bilateral loss ("gold standard"). Can determine whether reduced caloric responses are due to inadequate stimulation or true vestibular loss. Can assist with therapeutic decisions. May demonstrate residual function in the absence of caloric responses on ENG. Reflects dynamic compensation.	No selective targeting of each ear. Little consensus on abnormality. Not widely available. May miss unilateral or asymmetrical dysfunction. No standardisation regarding stimulus and analysis techniques.	71%	54%
Posturography ^{46,48}	Evaluates relative contribution of sensory and motor components of balance.	Assesses abnormal patterns of postural control not accessible by testing VOR. Reflects dynamic compensation.	Equipment expensive. Not widely available.	50%	

a= Electronystagmography
b= Vestibulo-ocular reflex
c= Rotational chair

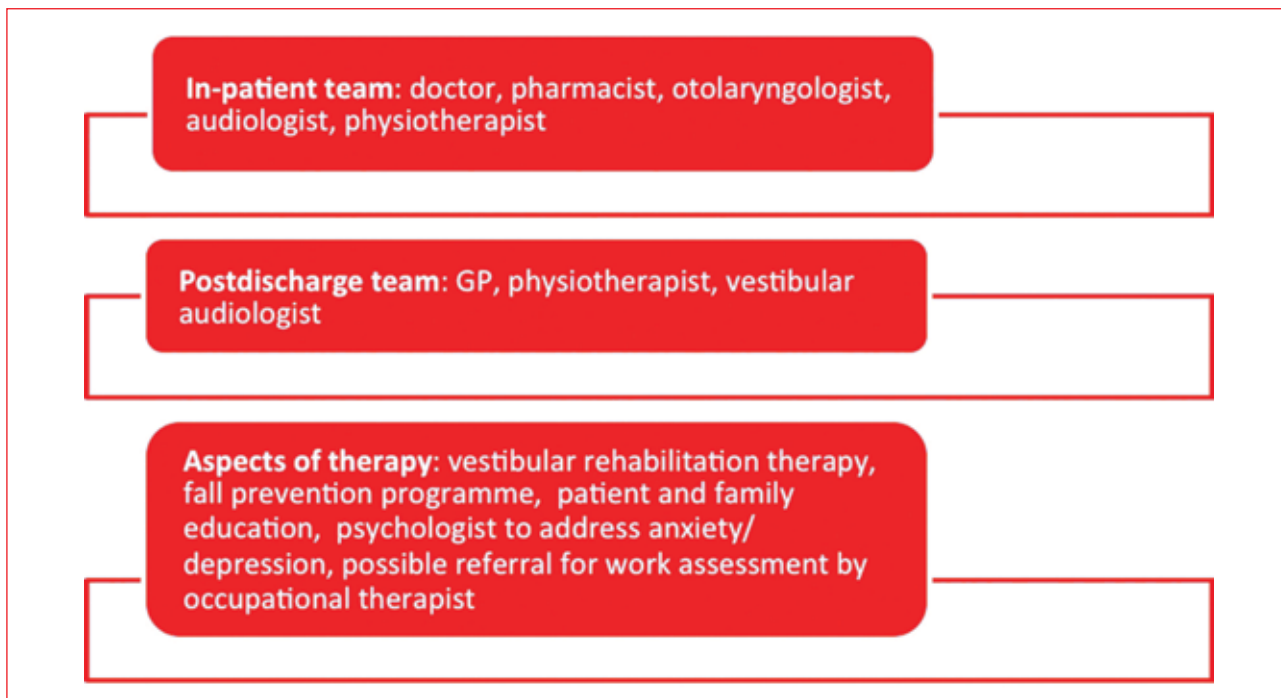


Figure 1: An idealised scheme of professionals and services required for the rehabilitation of a patient with vestibulotoxicity

While drugs, such as one of the selective serotonin reuptake inhibitors, may be indicated, it is suggested that these be used sparingly, as they are associated with side-effects of increased tinnitus, increased risk of falling and nausea.⁵⁰

Vestibular rehabilitation therapy

Vestibular rehabilitation therapy (VRT) has been a major step forward in the management of dizzy and vertiginous patients. This is especially important as medication is often unhelpful,⁵⁰ leaving VRT as the treatment of choice for particular disorders of balance and gait.

VRT is currently the only suitable treatment option for patients with vestibulotoxicity, but results are variable and sometimes disappointing. While not specific to vestibulotoxicity, there is some evidence that VRT introduced as soon as possible after the insult may result in a good outcome.⁵² The aims of VRT for vestibulotoxic patients are as follows: to ensure safety when moving, to prevent further deconditioning due to fear of falling and activity avoidance, and environmental and lifestyle management.²⁰ Although some improvement may be experienced, patients continue to be at risk of falling and report significant perceived physical impairment and disability.¹⁹ Gillespie and Minor⁵³ cite studies in which up to 50% of patients failed to respond to VRT. Patients with medical co-morbidities have a poorer prognosis for recovery than those without, probably due to deconditioning, which would prevent full participation in a VRT programme.^{53,54} However, age does not seem to be a significant obstacle to recovery.⁵²

Monitoring

As referred to earlier, there appears to be a lack of association between aminoglycoside dose or serum concentration and vestibulotoxicity, so even if levels are normal, damage may still occur. Furthermore, there is no single test that can predict or identify the presence of vestibulotoxicity, and as can be seen from Table II, the sensitivity and specificity of the available tests are suboptimal. Vasquez and Mattucci⁵⁵ recommend a flexible approach when monitoring patients for the effects of ototoxicity and suggest that even if bedside testing such as dynamic visual acuity and head thrust is the only method available to monitor patients, this is preferable to no monitoring at all, a view supported by others.^{3,4,16,56} It should be noted that monitoring should continue after the drug has been withdrawn, as, in many cases, symptoms first appear after discharge. Figure 1 presents an idealised scheme of the professionals and services that could be involved in the holistic care of the patient undergoing treatment with aminoglycosides.

Conclusion

The continued use of aminoglycosides has stimulated a desire to understand the mechanism of ototoxicity and to develop strategies to reduce the ototoxic potential of these drugs.⁵⁷ While the usual rationale for the administration of aminoglycosides is to save the life of a seriously ill patient, it has been suggested that patients and their families may not always be advised of the ototoxic potential of these drugs.²¹ It is possible that this is due to a lack of awareness on the part of the prescribing clinician, which is then compounded by a lack of awareness of symptoms of ototoxicity during

the course of treatment. Although alternative drugs are available, cost and other factors may still influence choices. In view of the permanent and extremely disabling effects of aminoglycosides and their continued common use, this debate needs to be moved into the everyday clinical arena as a matter of urgency.

Conflicts of interest

The authors declare no conflict of interest.

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