Oscillopsia and dizziness resulting from Gentamicin antibiotic treatment:

A clinical note on the beneficial effects of vestibular rehabilitation therapy

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Oscillopsia, defined as the apparent movement of the visual world, is a condition which may result from lesions at any point along the vestibulo-ocular reflex pathways. Dizziness, a sensation of postural instability, often accompanies oscillopsia and leads to difficulty moving ('ataxia'). Oscillopsia and dizziness are particularly severe when they are caused by a bilateral loss of function of the vestibular receptor cells in the inner ear, such as sometimes occurs with the use of aminoglycoside antibiotics, e.g, gentamicin. This class of antibiotics must be used for some kinds of potentially life-threatening bacterial infections; however, vestibular receptor cell loss ('vestibulotoxicity') often results, leading to the development of oscillopsia, dizziness and other signs of bilateral vestibular damage. The purpose of this short review is to summarise the most recent data on gentamicin vestibulotoxicity and the various treatment options. It is concluded that drug therapy is of no benefit in the case of vestibulotoxicity and that vestibular rehabilitation therapy is the only effective treatment option.

Human spatial orientation is dependent upon the integration of sensory information from multiple sensory systems, in particular the visual system and the vestibular system located in the inner ear. Reflexive eye movements such as the optokinetic reflexes (OKRs) and vestibulo-ocular reflexes (VORs) are essential in order to stabilize gaze and to perceive the world as stationary during head movement, as well as to maintain postural stability (see Howard, 1981; Baloh & Honrubia, 1990, for reviews). The vestibular receptor cells in the inner ear ('vestibular labyrinth') transmit head movement information via the VIIIth cranial nerve, to neurons in the brainstem vestibular nucleus, some of which project directly to motoneurons engaged in the generation of eye movement (see Wilson & Melvill Jones, 1979 for a review). Visual information is also known to converge on vestibular nucleus neurons via the accessory optic tract, the inferior olive and the cerebellar flocculus (see Baloh & Honrubia, 1990 for a review). Neuronal studies have shown that optokinetic stimulation in the absence of head movement can induce firing patterns in vestibular nucleus neurons which are similar (but not identical) to those induced by actual head movement (e.g, Henn, Young & Finlay, 1974). It is this integration of visual input with vestibular information conveyed to the vestibular nucleus from the labyrinths, that allows the OKRs and VORs to generate compensatory eye movements in response to a broad range of head movement velocities and frequencies (Howard, 1981).

Since the stabilization of gaze during head movement relies on the integrity of the OKRs and VORs, lesions of the labyrinth, the cerebellum or the vestibular nucleus result in the apparent movement of the visual world during head movement, a condition known as 'oscillopsia' (e.g, Zee, Yee & Robinson, 1976; McConnell, Darlington, Smith, Sturge, Thomson, Nukada & Mair, 1990; see Baloh & Honrubia, 1990 for a review). Oscillopsia is often associated with dizziness - the sensation of postural instability - and usually results in difficulty moving ('ataxia') (Herdman, Sandusky, Hain, Zee & Tusa, 1994; see Baloh & Honrubia, 1990 for a review).

Oscillopsia and dizziness due to aminoglycoside antibiotics

Although oscillopsia and dizziness can be caused by lesions at any point along the vestibular reflex pathways (e.g, a tumour located on the VIIIth nerve or in the vestibular nucleus), one of the most frequent causes is treatment with a particular class of antibiotics known as aminoglycoside antibiotics. Aminoglycoside antibiotics such as streptomycin, gentamicin, kanamycin and neomycin are widely used and effective against a range of bacterial infections and are often prescribed for potentially life-threatening conditions such as bacterial cardiomyopathy (Tange, Dreschler, Prins, Buller, Kuijper & Speelman, 1995). In such cases there is no reasonable alternative to the prescription of these antibiotics. However, aminoglycosides can have potentially toxic effects in the kidneys ('nephrotoxicity') and in the inner ear, particularly affecting the vestibular receptor cells ('vestibulotoxicity') (see Wersall, 1995 for a review). Gentamicin is one of the most commonly prescribed aminoglycoside antibiotics in New Zealand and Australia and is among the most toxic to vestibular receptor cells (Halmagyi, Fattore, Curthoys & Wade, 1994). It is estimated that nephrotoxicity occurs in up to 17%, and vestibulotoxicity in up to 11%, of patients treated with gentamicin (Tange et al., 1995). In a recent review, Halmagyi et al. (1994) concluded that there is no safe dose of gentamicin in relation to the vestibular system. In their evaluation of 36 patients who had received gentamicin treatment and subsequently presented with bilateral vestibular receptor cell damage, Halmagyi and colleagues found 16 patients who had received less than the maximum recommended dose. The vestibulotoxicity could not be explained purely in terms of reduced elimination of gentamicin due to nephrotoxicity, since patients showing signs of nephrotoxicity had the gentamicin dose reduced and still sustained vestibular damage (Halmagyi et al., 1994). One of the alarming findings from this study was that in 32 out of the 36 cases, gentamicin vestibulotoxicity was not recognised by the attending physicians before the patients were discharged from hospital. Halmagyi and colleagues noted that many of the physicians were unfamiliar with aminoglycoside vestibulotoxicity and looked for signs of unilateral rather than bilateral vestibular damage. Since the antibiotic is administered systemically and therefore will be distributed to both inner ears, the vestibular receptor cells should be affected approximately equally in the two vestibular labyrinths and therefore unilateral symptoms such as vertigo (ie. the illusion of self-motion) and ocular nystagmus will not be present. In some cases, gentamicin toxicity was excluded by physicians on the basis of normal hearing, and yet gentamicin is known to have little effect on hearing within the speech frequencies, 1 to 3 kHz (Halmagyi et al., 1994). Since many physicians are not familiar with the symptoms of vestibulotoxicity and description of the perceptual experiences of oscillopsia and dizziness is problematic because of the absence of a suitable vocabulary, such patients are sometimes referred to clinical psychologists for psychological/ psychiatric assessment. Therefore, it is worthwhile for the clinical psychologist to become familiar with oscillopsia and dizziness as signs of vestibular impairment, just as he/she is familar with a range of other visual (e.g, colour blindness), auditory (e.g, tinnitus) and somesthetic (e.g, phantom limb pain) sensory abnormalities.

Symptoms of gentamicin vestibulotoxicity

Because gentamicin will affect both inner ears and the vestibular damage will be bilateral, the symptoms of vestibulotoxicity result from the absence of normal vestibular reflexes and visual/vestibular perceptions rather than the presence of abnormal vestibular responses arising from an asymmetry in vestibular function (as in the case of unilateral damage). Since loss of function of the vestibular receptor cells will cause abnormal responses in vestibular nucleus neurons in the brainstem, the OKRs, VORs, vestibulo-spinal reflexes and the vestibulo-cortical pathways responsible for vestibular perceptions, will all be affected (Smith & Curthoys, 1988; Smith & Curthoys, 1989; Curthoys & Halmagyi, 1995). The OKRs will show reduced amplitude in relation to the visual stimulus (ie. reduced 'gain') as well as abnormal timing ('phase') (Zee, Yee & Robinson, 1976). The VORs, as tested in darkness, will either not be generated at all or else, in the case of partial bilateral vestibulotoxicity, the gain re head movement will be markedly reduced and the phase will be abnormal (Halmagyi & Curthoys, 1987). Although humans are less reliant on the vestibulo-spinal reflexes than lower mammals, vestibular damage nonetheless results in postural instability (Herdman et al., 1994). The ocular motor deficits give rise to the perceptual experience of oscillopsia, since when the head is moved under normal visual conditions, neither the OKRs nor the VORs will compensate for head movement as they normally would. Instead, the person will experience a 'slipping' of the retinal image in the direction of head movement. This visual experience is so debilitating that some patients suffering from oscillopsia become house-bound. The best simulation of the experience of oscillopsia is to view video footage recorded using a camera which has been carried without any attempt to steady it: the result is a visual image which literally 'bounces' in every direction. The most descriptive personal account of what it is like

to live with oscillopsia was written by a physician named 'JC'who diagnosed his own vestibulotoxicity following streptomycin treatment for tuberculosis during the second World War (JC, 1952). In addition to oscillopsia, patients with vestibulotoxicity often also experience dizziness, due to the disruption of the vestibulo-spinal and vestibulo-cortical pathways; together with the other reflex deficits, this results in a generalized difficulty in moving ('ataxia') (see Halmagyi & Curthoys, 1995 for a review). The movement of objects, such as passing cars, in the visual field is often severely disorienting, making crossing intersections or walking along busy streets particularly hazardous.

Why clinical psychologists need to know about aminoglycoside vestibulotoxicity

Although, at first glance, aminoglycoside vestibulotoxicity might seem solely the province of the neurologist and otolaryngologist, there are several reasons why clinical psychologists need to be aware of such phenomena. First, patients with vestibular impairments often suffer from anxiety and depression relating to their disability; it is also well established that such psychological disorders have a major impact on their ability to cope with oscillopsia and dizziness (Blakley, Barber, Tomlinson, Stoyanoff & Mabel, 1989; Telian, Shepard, Smith-Wheelock & Kemink, 1990; Cohen, 1992; Shepard & Telian, 1995). Second, because many patients with anxiety disorders (e.g, panic disorder, phobias) suffer from dizziness of unknown origin (Baloh, 1995; Rascol, Hain, Brefel, Benazet, Clanet & Montastruc, 1995; Shepard & Telian, 1995), care needs to be taken in distinguishing between patients with an anxiety disorder and related, non-vestibular dizziness, and patients with dizziness resulting from vestibular impairment who suffer from an anxiety disorder as a consequence (Baloh, 1995). Interestingly, some patients who experience dizziness as a result of panic disorder or phobia have been found to benefit from vestibular rehabilitation therapy (Shepard & Telian, 1995). Dizziness can also be a side effect of orthostatic hypotension (reduced blood pressure as a result of changes in posture) and many drugs, including antihypertensives, antipsychotics, antidepressants, vasodilators and anti-Parkinsonian drugs (Rascol et al., 1995). The clinical psychologist needs to be aware of the various possible causes of dizziness so that if it appears to be the primary problem, the appropriate referral can be made to a neurologist or otolaryngologist (Baloh, 1995). Many specialists recommend close contact between neurologists, otolaryngologists, psychologists and psychiatrists in the diagnosis and treatment of dizziness (Shepard & Telian, 1995).

Treatment for oscillopsia and dizziness

It was once believed that vestibular receptor hair cells could not regenerate once damaged. In fact, mild to moderate gentamicin vestibulotoxicity is reversible, provided that the treatment is stopped in time (Black, Peterka & Elardo, 1987); hence it is critical that the signs of vestibulotoxicity are recognised. It has recently been reported that, under some circumstances, guinea pig and human vestibular receptor cells may reappear some months following severe gentamicin vestibulotoxicity (Forge et al., 1993; Warchol et al., 1993; Rubel et al., 1995). However, currently there is disagreement over whether these receptor cells are actually new cells or whether they are supporting cells that have been genetically transformed (e.g, Rubel et al., 1995). Most importantly, it has not yet been confirmed that the regenerated receptor cells are functional (Rubel et al., 1995). Nonetheless, the excitement surrounding the discovery that these receptor cells can regenerate under some circumstances has led to speculation that it may be possible to further stimulate recovery through drug treatment or gene therapy (see Lambert, 1994 for a review). However, it must be emphasised that these treatment possibilities are at a very early stage of development and have yet to be fully investigated.

At present, there are no effective drug treatments for oscillopsia and dizziness arising from gentamicin vestibulotoxicity. Because, in this case, they are due to the *absence* of normal vestibular function rather than the *presence* of abnormal vestibular responses (ie. as in the case of unilateral vestibular damage), it is unlikely that any specific drug treatment could be developed (Smith & Darlington, 1994). Drugs such as benzodiazepines (e.g, diazepam), which are sometimes prescribed for vertigo and dizziness (see Baloh, 1994 for a review), are unlikely to provide symptomatic relief, although their anxiolytic effects may provide some comfort at the expense of significant sedation (see Rascol et al., 1995 for a review).

It is generally agreed that the only effective treatment for oscillopsia, dizziness and the other symptoms of gentamicin vestibulotoxicity is vestibular rehabilitation therapy (see Foster, 1994 for a review). First described by Cawthorne (1944) and Cooksey (1945), the general principle behind vestibular rehabilitation therapy is that the brain can be retrained to cope with an impaired vestibular system by subjecting the patient to a specific set of intensive exercises involving head movement. Although there are various programs used in different countries throughout the world, the exercises generally involve sets of repetitive head movements in all planes of space, gradually

increasing in amplitude and speed (e.g, Cohen, Kane-Wineland, Miller & Hatfield, 1995; see Foster, 1994 for a review). In addition to increasing the adaptation of the patient to the unusual visual stimulation resulting from vestibular impairment (Cohen, Kane-Wineland, Miller & Hatfield, 1995), patients gradually learn to substitute other kinds of eye movement (e.g, smooth pursuit and cervico-ocular reflex eye movements) for the deficient OKRs and VORs and also learn specific strategies to restrict their head movement under certain circumstances (Halmagyi & Curthoys, 1987; see Foster, 1994 for a review). One of us (CD) is currently using vestibular rehabilitation therapy to treat patients suffering from gentamicin vestibulotoxicity in the Clinical Psychology Research and Training Centre in the Department of Psychology at the University of Otago in Dunedin. As in other centres (e.g, Cohen et al., 1995), we have found that, even over 4 weeks, such therapy can help patients adapt to their impaired vestibular function.

It is our contention that the symptoms of gentamicin vestibulotoxicity must become more widely recognised, both for the purpose of preventing further toxicity, if possible, and also in order to adequately treat symptoms such as oscillopsia and dizziness once the aminoglycoside treatment has finished (Halmagyi et al., 1994). Since surgical and drug treatments are of little use in this circumstance, vestibular rehabilitation programs are the only viable option and their effectiveness is well established (Cohen et al., 1990; Cohen, 1992; Horak et al., 1992; Shepard et al., 1993; Cohen et al., 1995; see Foster, 1994 for a review). Clinical psychologists are becoming increasingly involved in the treatment of neurological as well as psychiatric disorders. Therefore, we suggest that they are well placed both to recognise the symptoms of gentamicin vestibulotoxicity and to participate in the delivery of a vestibular rehabilitation program.

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