

Critical Review:
Efficacy of Otoprotective Drugs in Preventing Noise Induced Hearing Loss

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This critical review examines the potential efficacy of otoprotective drugs in reducing noise induced hearing loss in humans. Study designs include: randomized controlled trials, cross-over, and a case control study. Overall, the examined research supports the use of magnesium supplementation in reducing temporary threshold and permanent threshold shifts in humans, however, length, intensity, and noise type along with dosage size and safety of extended use of supplements need to be studied further before recommendation for clinical use is proposed.

Introduction

Noise-induced hearing loss (NIHL) is considered to be one of the most common occupational health hazards. In the developed and developing nations, upwards of 600 million people are estimated to be working in environments with hazardous levels of noise with 50 to 60 million in the United States and Europe (Alberti, 1998). In the United States it is estimated that 10 to 15 million people, of all age groups, have NIHL. The annual cost in compensation to members of the US military is more than \$200 million (Boswell, 2004). NIHL is the leading cause of occupational disease, a significant cause of disability and a major cost to society.

Traditional prevention of NIHL is performed by reducing the sound energy entering the inner ear. Hearing conservation programs are essential, effective and significantly reduce NIHL but there are a number of conditions that may result in only partial implementation, for example, low compliance, poor fitting of hearing protective devices and/or financial incapacity (Attias et al., 2004).

Furthermore, noise exceeding the protective capabilities of the hearing protection device can also result in cochlear damage. Therefore, a drug designed to prevent and treat NIHL would be an important element in a comprehensive approach to maintaining cochlear function and integrity in individuals exposed to noise (Kopke, 2002).

While high-intensity noises impart sufficient energy to the cochlea to cause mechanical damage, noise exposure also causes metabolic challenges to the cochlea. Acoustic overexposure causes the production of reactive oxygen species (ROS), reactive nitrogen species (RNS) and other free radical molecules in the cochlea. These oxidative compounds are quite capable of inducing damage and loss of function when introduced into the cochlea (Kopke, 2002). Therefore, antioxidants that detoxify these free radicals, or agents that increase blood flow may serve to protect or rescue hair cells from NIHL. Otoprotective agents that occur naturally in the diet such as vitamins A, C and E and selenium have been shown to reduce NIHL in animals (Campbell, 2004). Other micronutrients, including

D-methionine (D-Met) present in fermented foods such as cheese and yogurt, N-acetyl cysteine (NAC) found in brussel sprouts, acetyl L-carnitine (ALCAR) and Idebenone have all been found to protect animals when administered before noise exposure (Ton and Parng, 2005, Kopke et al., 2005, Sergi et al., 2006).

Although all these agents have shown promise in reducing NIHL, they have only been studied using animal models. The most promising agents D-Met, ALCAR and NAC show good protection when administered before noise exposure, D-Met and ALCAR have shown better hair cell protection than NAC.

Objectives

The objective of this review was to evaluate critically the existing literature regarding the efficacy of otoprotective drugs to protect against noise induced hearing loss in humans.

Methods

Search Strategy

Computerized databases, including PubMed, ComDis Dome, MEDLINE-Ovid, Cochrane Library, EMBASE and CINAHL, were searched using the following search parameters:

((noise-induced hearing loss) **OR** (NIHL)) **AND** ((otoprotective) **OR** (antioxidant) **OR** (drugs) **OR** (pharmacological)) **AND** (human).

Selection Criteria

Studies selected for inclusion in this critical review paper were required to investigate the impact of any pharmacologic agents on hearing loss associated with noise trauma in humans.

Data Collection

The database search yielded four studies that met the aforementioned selection criteria.

Results

Attias *et al.* (1994) examined whether the long term supplementation of magnesium would reduce noise induced permanent threshold shifts (PTS) in humans exposed to repeated impulse noise. A randomized, double-blind, placebo-controlled design was conducted with 300 males in military training. Training included repeated exposures to high levels of impulse noises with an average intensity of 164 dBA and main energy between 2 to 5 kHz. Auditory threshold measurements (air and bone) and blood samples were collected before and 7 to 10 days after the last exposure. Each subject's pre- and post- study blood magnesium levels in serum (SMg), red cells (EMg), and mononuclear cells (MMg) were determined.

The differences in incidence of PTS, defined as a threshold greater than 25 dBHL, between the two groups were statistically significant. A placebo group demonstrated more frequent and worse PTS than the magnesium group. Magnesium levels of the two groups prior to exposure were similar. Post-exposure values of MMg in both groups were significantly different. For each auditory frequency tested, lower magnesium levels were measured in subjects with PTS compared to those without PTS. The Mantel-Haenszel chi-square test for linear trend was significant, indicating that as the magnesium level decreased, the incidence of PTS increased.

Attias *et al.* (2004) investigated

the effects of magnesium (Mg) intake on reversible cochlear alteration using temporary threshold shift measures. A same subject, double-blind, placebo controlled cross-over study was conducted using 20 male subjects with normal bilateral audiometric thresholds and distortion product otoacoustic emissions (DPOAEs). All subjects participated in three recording sessions: an initial baseline prior to any agent intake, followed with 10 days of placebo ingestion taken on a daily basis, and then 10 days of 122 mg Mg ingestion. Each subject's pre- and post- study Mg levels were determined. All subjects were exposed to 90 dB SL (sensation level) white-noise for 10 minutes. Auditory thresholds were measured prior to and immediately after noise exposure.

After Mg intake, temporary threshold shifts (TTS) at each frequency was lower than after placebo intake. No significant differences were found between TTS measured post-placebo intake and those measured prior to intake. Unlike the behavioural TTS, the OAE shifts did not change in a set pattern as a function of frequency for the three test phases. However, at all frequencies the OAE shift associated with the post-Mg phase was distinctly lower compared with the OAE recorded prior to intake and post-placebo. The level of Mg measured was on average higher at the post-Mg recording session than the no-intake session.

Kramer *et al.* (2006) examined the efficacy of a single dose of N-acetylcysteine (NAC) in reducing temporary threshold shifts induced by loud music. A randomized, double-blind, placebo-controlled design was utilized on 32 subjects with normal pure-tone thresholds and distortion product otoacoustic emissions (DPOAEs). Half

the participants were given NAC and the others were given a placebo 30 minutes prior to entering a nightclub.

Pure-tone thresholds and DPOAEs were collected before and after two hours of live music exposure. One participant from each group was given a dosimeter to automatically record the average level (dBA) of noise exposure during a two hour session. Dosimeter readings ranged from 92.5 to 102.8 dBA, with a mean of 98.1 dBA. Immediately following exposure the participants had their pure-tone thresholds and DPOAEs tested.

Greater levels of TTS were found for 3, 4, and 6 kHz with the largest shift at 4 kHz. Repeated measures analysis of variance showed no significant difference between NAC and placebo subjects. No significant interactions were found for DPOAEs, and the main effects were not significant for ear, treatment, or frequency.

The study conducted by Walden *et al.* (2000) addressed whether natural levels of serum magnesium (SMg) in soldiers is a determining factor in susceptibility to noise-induced hearing loss. A case control design study using 68 male soldiers with similar military service records involving frequent exposure to high-level weapon noise was conducted. A written survey detailing the chronology of noise exposure history, air and bone conduction auditory thresholds and serum magnesium levels were collected for each participant. The primary analysis consisted of correlations computed between audiometric and body Mg measures. The correlation between PTA to Mg levels was not statistically significant.

Conclusions

At present, only two supplements with otoprotective abilities in animals (NAC and magnesium) have been tested on humans. Experimental research suggests a potential role for magnesium in protecting against NIHL, however, NAC has shown no such preventive ability.

The methodological limitations of the studies with regards to the type of noise exposure, length and intensity of exposure, along with the dosage size, time of dosage and long term effect of use of any supplement require further study before recommendation for use in a clinical setting is proposed. Other factors that require consideration would include the cost of use of a supplement in conjunction with current hearing conservation programs.

One difficulty in studying the protective ability of any supplement arises from the ethical problems caused by exposing humans to known sources of noise that can cause NIHL.

Until more definitive information is available, treatment with any supplement should not be proposed for clinical use.

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