Oral pharmacologic otoprotective agents to prevent Noise-Induced Hearing Loss (NIHL): When dietary concentration isn't enough

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"DRUGS" VERSUS "NUTRACEUTICALS"

A number of oral pharmacologic protective agents for noise-induced hearing loss are in or approaching clinical trials. The demarcation between a nutraceutical and a drug is not always clear. Broadly, the definition of a drug includes "any chemical substance that affects living processes in a positive or negative manner". However that definition is not the legal or regulatory definition. While each country has its own approval processes, the general approach is frequently similar to that in the United States. In the United States, a molecule or compound is classified as a drug if it is "used to treat or prevent a medical disorder". As a drug, these pharmacologic agents are subject to the Pure Food and Drug act of 1906 requiring a list of ingredients, standards for preparation, registration of dangerous or addictive drugs, and prohibition of false or misleading claims. The Sherley Amendment of 1912 prohibited fraudulent therapeutic claims for patent medications, and the 1938 Federal Food, Drug and Cosmetic Act mandated that drugs could not be sold until they had been tested for safety and all labeling was accurate and complete. In 1951, The Durham Humphrey Amendment specified how drugs could be ordered and dispensed and for the first time limited new drugs to investigational use only. Further, for the first time, a separate category for over the counter (OTC) drugs was specifically created. The OTC classification is designated primarily on the basis of safety. Essentially, OTC drugs are deemed sufficiently safe that they do not need direct medical supervision and can be sold directly to the patient without physician direction. For some drugs both prescription and OTC forms are available with the distinction frequently being in dosing or method of administration. For a review the reader is referred to (Meldrum 2007) Thus agents classified as "drugs" must meet the following standards:

1) The ingredients must be listed.

2) They must meet standards for preparation.

3) They may not make false or misleading claims, including false therapeutic claims.

4) They must be tested for safety.

5) All labeling must be accurate and complete.

6) They are subject to laws regulating how they can be ordered and dispensed.

7) New drugs are limited to investigational use only and cannot be sold until approved by the Food and Drug Administration (FDA).

8) The FDA approval specifies whether the drug is available by prescription only or can also be sold OTC and if so at which dose and in which specific formulation.

The FDA approval is extensive. Current estimates are that, on the average, it takes a drug approximately 15 years and over 1 billion US dollars to go from bench to bedside including FDA approval for marketing.

Thus while expensive and time consuming, an agent classified and FDA approved as a drug affords the consumer many protections and assurances.

Nutraceuticals and dietary supplements are not subject to the same regulations as drugs even though some may have some of the same ingredients as "drugs". Nutraceuticals may be advertised with the disclaimer "not intended to diagnose, prevent, cure, or treat any medical disorder" to avoid being classified as a drug. Frequently they are labeled "to promote hearing health" or similar language. Nutraceuticals fall under the Dietary Supplement Health and Education Act (DSHEA) of 1994. The FDA does have the authority to limit claims under DSHEA regarding therapeutic efficacy and labeling but because they are classified as "foods" many, if not most, are not reviewed by the FDA. As foods, they do not have to prove safety or efficacy. Herbal medications are also classified as dietary supplements and thus no testing for safety or efficacy is required. Because the distinction between drug and nutraceutical can be complex, for some agents manufacturers may seek, or be required to seek, an FDA exemption to ensure that the FDA does not consider it to be a drug, subject to the above listed regulations. Sometimes an exemption can be granted on the basis of the compound's known safety but an exemption does not guarantee efficacy or allow it to be marketed as a drug.

For drugs, the FDA approval process requires that the potential side effects and drug interactions be listed. Although nutraceuticals, dietary and herbal supplements, and even foods themselves, may also have side effects and adverse drug interactions with the patients' other medications, no testing, listing or specification of them is required.

Complementary and integrative medicine, which includes nutraceuticals is gaining much more widespread acceptance in Westernized countries but the consumer should be aware, that while they may be very effective in some cases, they do not carry the same degree of regulation and assurances (see reviews by Seidman & Moneysmith 2007; Meldrum 2007). However because they are not subject to the expensive FDA approval process, they have the potential to be less expensive and progress more quickly to the marketplace.

Interestingly, all the oral "drugs" in or approaching clinical trials to prevent noise-induced hearing loss are antioxidants, also present in foodstuffs. However they may be classified as a drug on the basis of the claims being made to prevent or treat noise-induced hearing loss, or on the basis of containing concentrations above the usual levels of diet or dietary supplements. Companies may seek FDA approval so that they may market the compound with the specific claims and safety assurances that approval allows.

This review is restricted to compounds that can be given orally. While some agents are being developed that cannot be safely administered systemically and can only be given via round window administration, their clinical acceptance to routinely prevent or rescue from noise-induced hearing loss is probably limited. The costs and risks of repeated round window drug administration could also be problematic for noise-induced hearing loss. Further patient acceptance and compliance are always major factors for any medical treatment.

Antioxidants that are present in foodstuffs have a number of advantages. Frequently as a component of food, their bioavailability, absorption, and distribution through the gastric pathway are known. Usually their safety profile including safety ranges, and effects of high dosing over long periods of time in a number of species have already been studied, in some cases for decades in both human and animal nutrition studies.

Interactions with other drugs or in specific patient populations such as pediatric or geriatric populations are also frequently known.

Although all of the following agents are antioxidants, they do not all have the exact same mechanisms. The general classification of antioxidant indicates that the agent either directly donates an electron (direct antioxidant) or facilitates other compounds (e.g. glutathione) donating an electron (indirect antioxidant) to the unpaired electrons of the outer shell of free radicals, thus stabilizing it. Some agents are both direct and indirect antioxidants. For many agents, the mechanisms of protection are still being elucidated.

The antioxidants that are currently in or approaching clinical trials through the FDA clinical trials and approval process, to prevent noise-induced hearing loss include D-methionine (D-met), ebselen, and N-acetylcysteine. All of these agents can be delivered orally.

D-MET

Clinical trials

D-met is approaching clinical trials with the US Army to prevent noise-induced hearing loss in drill sergeant instructor trainees during their required M-16 weapons training. These clinical trials are funded through a grant from the US Department of Defense. Although D-met can be effectively delivered through the round window (Korver et al. 2002; Wimmer et al. 2004) and by injection (Campbell et al. 1996; Kopke et al. 2002; Sha & Schacht 2000) for various applications, for clinical trials the current formulation is an orange flavored oral suspension with flavor matched placebo (Hamstra et al. 2010) which has been prepared according to the FDA Good Manufacturing Practices (GMP) standards. A Phase 1 manuscript has been published (Hamstra et al. 2010) and 2 small scale Phase 2 clinical trials were conducted in India demonstrating protection from radiation induced oral mucositis (in preparation for publication) and from cisplatin-induced hearing loss (Campbell et al. 2009). The preparation is stable for at least 18 months at 40 degrees centigrade, which can be particularly useful for military settings. A human dose is approximately a teaspoonful depending on subject weight.

Although D-met is a component of fermented proteins such as cheese and yogurt, the clinical trials are going through the FDA approval process.

Protection in animal studies

Animal studies using prophylactic D-met administration in chinchillas (Kopke et al. 2002; Campbell et al. 2007), mice (Samson et al. 2008) and guinea pigs (Cheng et al. 2008) have been conducted in a variety of laboratories confirming virtually complete protection from permanent noise-induced hearing loss cochlear outer hair cell loss at least for the noise exposures used in those studies (Cheng et al. 2008), Campbell et al. 2009). Protection from permanent threshold shift has been consistent across studies (Kopke et al. 2002; Campbell et al. 2007; Cheng et al. 2008; Samson et al. 2008). No studies have shown a lack of protection or exacerbation of noise-induced hearing loss.

However, protection from hearing threshold shift within the first 24 hours after noise exposure has produced variable results across studies. Cheng et al. (2008) reported virtually complete D-met protection from noise-induced threshold shift 24 hours after

noise exposure in guinea pigs after a 10 minute 105 dB noise exposure and again after 7 days. However Kopke et al. 2002 reported no significant D-met protection 24 hours after noise exposure in chinchillas after a 6 hour 105 dB SPL noise exposure although D-met provided virtually complete protection from permanent threshold shift 21 days after noise exposure in those same animals. Samson et al. (2008) reported no significant D-met protection 24 hours after noise exposure but with complete protection from permanent noise-induced threshold shift both at 14 and 21 days after a 4 hour 110 dB noise exposure. It would appear that protection from threshold shift 24 hours after noise exposure may vary by species and type of noise exposure while protection from permanent threshold shift occurs irrespective of species, at least in studies reported to date. Dosing protocols have also varied. Cheng administered 300 mg/kg D-met to guinea pigs one hour before and one hour after the noise exposure. Samson et al. (2008) also delivered the D-met one hour prior to and one hour after noise exposure but used 400 mg/kg in mice. Kopke et al. (2002), used a lower dose but for a longer time period in chinchillas, administering 200 mg/kg D-met twice per day starting 2 days prior to noise exposure and continuing 2 days after noise exposure. Campbell et al. (2007) also reported almost complete rescue from permanent threshold shift first administering D-met one hour after a 6 hour 105 dB SPL noise exposure and then continuing twice per day for another 2 days. Further first administration of D-met can be delayed for up to 7 hours after noise exposure and still provide significant protection from outer hair cell loss and permanent threshold shift (Campbell et al. 2009). Thus it appears that D-met protection and rescue from permanent noise-induced hearing loss is consistent across noise exposures used thus far, across a variety of species, and for a wide range of dosing protocols. However protection from noise-induced threshold shift at 24 hours may vary by species, noise exposure or dosing protocol.

Multiple animal studies have also documented D-met's efficacy as a protective agent against cisplatin-induced hearing loss (Campbell et al. 1996, 1998) aminoglycoside-induced hearing loss (Sha & Schacht 2000) and radiation induced oral mucositis (Vuyyuri et al. 2008). Because some patients are exposed to one or more of these in addition to noise-exposure, an agent that is cross-protective may be advantageous for some patients.

EBSELEN

Clinical trials

Sound Pharmaceuticals is planning Phase 2 clinical trials at Camp Pendleton, San Diego, California for protection from noise-induced hearing loss in Marines undergoing their artillery training. Phase 2 clinical trials for protection from temporary threshold shift in humans are also in the planning stages. Ebselen, a selenium based compound, is currently formulated for oral administration, according to FDA GMP standards, as a dry blend capsule with matched placebo. In addition they are planning clinical trials in Seattle to protect against cisplatin-induced hearing loss. No clinical trials have yet initiated for either application but they are going through the FDA approval process for them.

Protection in animal studies

Studies in both rats and guinea pigs have consistently shown either partial or complete protection from permanent noise-induced hearing loss (Pourbakht & Yamasoba 2003; Yamasoba et al. 2003, 2005; Lynch et al. 2004; Lynch & Kil 2005; Kil et al. 2007). As for D-met, no study has reported a lack of protection or exacerbation of noise-induced hearing loss. Significant reduction in temporary threshold shift 3 hours after noise exposure in guinea pigs has been reported (Yamasoba et al. 2005) but no other study has reported findings for temporary threshold shift with ebselen.

For permanent noise-induced threshold shift, ebselen provided incomplete but significant protection from a 4 hour, 110, 113 or 115 dB SPL, 4-16 kHz noise band noise exposures in rats. (Lynch et al. 2004; Lynch & Kil 2005; Kil et al. 2007). In guinea pigs, significant protection from permanent noise-induced threshold shift was also reported after a 5 hour 125 dB SPL 4 kHz octave band noise exposure.

N-ACETLYCYSTEINE (NAC)

Clinical trials

NAC has been long studied as a putative agent to protect against noise-induced hearing loss. However in 4 clinical trials conducted to date, none have shown significant protection from either temporary or permanent noise-induced hearing loss (Toppila et al. 2002; Kramer et al. 2006; Balough 2011). Topilla et al. (2002), using 400 mg NAC per day, and Kramer et al. (2006) using 900 mg NAC per day and tested subjects hearing before and after exposure to night club noise. Neither study showed significant NAC protection. At Camp Pendleton two prospective, randomized placebo controlled clinical trials were conducted (Balough 2011) in Marine recruits during either 2 weeks or 16 days of weapons training. Either 900 mg of NAC or placebo was administered 3 times per day starting 2 days before weapons training and continuing 3 days after weapons training (study 1) or 2 grams of NAC twice per day (study 2). Final hearing tests were conducted 2 weeks (study1) or 10 days (study 2) after cessation of weapons training. The only side effect was excessive flatulence, possibly secondary to the fizzy tab formulation of their oral preparation. They concluded that although their clinical trials site using the Marine recruit population was optimal for testing otoprotective agents, NAC was not an effective otoprotective agent for noise-induced hearing loss even at the 4g/day dose of study 2 which is the upper level of feasibility for NAC oral delivery due to drug compounding considerations. Reportedly, the Department of Defense does not plan further testing for NAC as an otoprotective agent for noise-induced hearing loss.

Animal studies

Although NAC is one of the most widely studied agents for protection from noise-induced hearing loss, results across studies are not in agreement. Although some studies have shown at least partial protection from noise-induced hearing loss (Ohinata et al. 2003; Bielefeld et al. 2007; Lorito et al. 2008; Fetoni et al. 2009) other studies have demonstrated no protection (Hamernik et al. 2008) or even exacerbation of noise-induced hearing loss (Duan et al. 2004). In some cases, protection from noise-induced hearing loss attributed to NAC may have been secondary partially or completely to a concomitant agent. (Huang et al. 2000; Kopke et al. 2002, Liu et al. 2001), reported NAC protection from NIHL but only when combined with high dose salicylate, which in itself is otoprotective (Yu et al. 1999). Clinically high dose aspirin

is unlikely to gain clinical acceptance as an otoprotective agent because it cannot be safely used in children and because the required high doses may have gastrointestinal toxicities or exacerbate other bleeding. Although NAC alone has shown some otoprotection from noise-induced hearing loss in some animal studies (Kopke et al. 2005, 2007) with the negative results from clinical trials to date, it does not appear to be among the most promising agents to prevent or rescue from noise-induced hearing loss.

SUMMARY

In summary, several agents are going through the FDA approval process for clinical trials to prevent noise-induced hearing loss. Currently D-met and ebselen are in or approaching FDA approved clinical trials. They both have an extensive body of consistently positive animal data supporting their development. Hopefully one or more agents will be FDA approved for use in the next few years. As discussed in Dr. LePrell's paper, a number of nutraceuticals also show excellent promise. While nutraceuticals do not generally go through the FDA approval process, some compounds like ACE Mg are promising and are undergoing rigorous clinical trials to also ensure safety and efficacy. In the future the incidence and severity of noise-induced hearing loss may be reduced.

REFERENCES

Balough BJ (2011). Pharmacologic therapy for hearing loss: basic science to clinical trials. In: Sound Wave Symposium. San Diego, CA.

Bielefeld EC, Kopke RD, Jackson RL et al. (2007). Noise protection with N-acetyl-l-cysteine (NAC) using a variety of noise exposures, NAC doses, and routes of administration. Acta Otolaryngol 127: 914-919.

Campbell KC, Rybak LP, Meech RP et al. (1996). -methionine provides excellent protection from cisplatin ototoxicity in the rat. Hear Res 102: 90-98.

Campbell KC, Meech RP, Rybak, LR et al. (1999). D-Methionine protects against cisplatin damage to the stria vascularis. Hear Res 138: 13-28.

Campbell KC, Meech RP, Klemens JJ et al. (2007). Prevention of noise- and drug-induced hearing loss with D-methionine. Hear Res 226: 92-103.

Campbell KCM, Nayar R, Borgonha S et al. (2009). Oral D-methionine significantly Protects against cisplatin induced hearing loss in humans. Association for Research in Otolaryngology, Baltimore, MD, Abstracts of the Thirty Second Annual Midwinter Research Meeting of the Association for Research in Otolaryngology 32:7, abstract #22.

Cheng PW, Liu SH, Young YH et al. (2008). Protection from noise-induced temporary threshold shift by D-methionine is associated with preservation of ATPase activities. Ear Hear 29: 65-75.

Duan M, Qiu J, Laurell G et al. (2004). Dose and time-dependent protection of the antioxidant N-L-acetylcysteine against impulse noise trauma. Hear Res 192: 1-9.

Fetoni AR, Ralli M, Sergi B et al. (2009). Protective effects of N-acetylcysteine on noise-induced hearing loss in guinea pigs. Acta Otorhinolaryngol Ital 29: 70-75.

Hamernik RP, Qiu W, Davis B (2008). The effectiveness of N-acetyl-L-cysteine (L-NAC) in the prevention of severe noise-induced hearing loss. Hear Res 239: 99-106.

Hamstra DA, Eisbruch A, Naidu MU et al. (2010). Pharmacokinetic analysis and phase 1 study of MRX-1024 in patients treated with radiation therapy with or without cisplatinum for head and neck cancer. Clin Cancer Res 16: 2666-2676.

Huang T, Cheng AG, Stupak H et al. (2000). Oxidative stress-induced apoptosis of cochlear sensory cells: otoprotective strategies. Int J Dev Neurosci 18: 259-270.

Kil J, Pierce C, Tran H et al. (2007). Ebselen treatment reduces noise induced hearing loss via the mimicry and induction of glutathione peroxidase. Hear Res 226: 44-51.

Kopke RD, Coleman JK, Liu J et al. (2002). Candidate's thesis: enhancing intrinsic cochlear stress defenses to reduce noise-induced hearing loss. Laryngoscope 112: 1515-1532.

Kopke R, Bielefeld E, Liu J et al. (2005). Prevention of impulse noise-induced hearing loss with antioxidants. Acta Otolaryngol;125: 235-243.

Kopke RD, Jackson RL, Coleman JK et al. (2007). NAC for noise: from the bench top to the clinic. Hear Res 226: 114-125.

Korver KD, Rybak LP, Whitworth C et al. (2002). Round window application of D-methionine provides complete cisplatin otoprotection. Otolaryngol Head Neck Surg 126: 683-689.

Kramer S, Dreisbach L, Lockwood J et al. (2006). Efficacy of the antioxidant N-acetylcysteine (NAC) in protecting ears exposed to loud music. J Am Acad Audiol 17: 265-278.

Lorito G, Giordano P, Petruccelli J et al. (2008). Different strategies in treating noiseinduced hearing loss with N-acetylcysteine. Med Sci Monit 14: BR159-BR164.

Lynch ED, Kil J (2005). Compounds for the prevention and treatment of noise-induced hearing loss. Drug Discov Today 10: 1291-1298.

Lynch ED, Gu R, Pierce C et al. (2004). Ebselen-mediated protection from single and repeated noise exposure in rat. Laryngoscope 114: 333-337.

Meldrum (2007). An introduction to pharmocology. In: Campbell K (ed): Pharmacology and ototoxicity for audiologists, pp 1-9. Clifton Park, NY: Thomson Delmar Learning.

Ohinata Y, MillerJM, Schacht J (2003). Protection from noise-induced lipid peroxidation and hair cell loss in the cochlea. Brain Res 966: 265-273.

Pourbakht A, Yamasoba T (2003). Ebselen attenuates cochlear damage caused by acoustic trauma. Hear Res 181: 100-108.

Samson J, Wiktorek-Smagur A, Politanski P et al. (2008). Noise-induced time-dependent changes in oxidative stress in the mouse cochlea and attenuation by D-methionine. Neuroscience 152: 146-150.

Seidman M, Moneysmith M (2007). Nutraceuticals and herbal supplements. In: Campbell KC (ed): Pharmacology and ototoxicity for audiologists (pp 57-69). Clifton Park, NJ: Thomas Delmar Learning.

Sha SH, Schacht J (2000). Antioxidants attenuate gentamicin-induced free radical formation in vitro and ototoxicity in vivo: D-methionine is a potential protectant. Hear Res 142: 34-40.

Toppila ESJ, Pyykko I, Miller JM (2002). Protection against acute noise with antioxidants. In: Nobel Forum, Karolinska Institutet, presented at Nordic Noise: An International Symposium on Noise and Health, Stockholm, Sweden.

Vuyyuri SB, Hamstra DA, Khanna D et al. (2008). Evaluation of D-methionine as a novel oral radiation protector for prevention of mucositis. Clin Cancer Res 14: 2161-2170.

Wimmer C, Mees K, Stumpf P et al. (2004). Round window application of D-methionine, sodium thiosulfate, brain-derived neurotrophic factor, and fibroblast growth factor-2 in cisplatin-induced ototoxicity. Otol Neurotol 25: 33-40.

Yamasoba T, Kondo K, Miyajima C et al. (2003). Changes in cell proliferation in rat and guinea pig cochlea after aminoglycoside-induced damage. Neurosci Lett 347: 171-174.

Yamasoba T, Pourbakht A, Sakamoto T et al. (2005). Ebselen prevents noise-induced excitotoxicity and temporary threshold shift. Neurosci Lett 380: 234-238.

Yu N, Li X, Hu B (1999). The effects of salicylate on noise-induced hearing loss in the guinea pig. Zhonghua Er Bi Yan Hou Ke Za Zhi 34: 344-346.