Efficacy of a combined drug therapy for ameliorating noise-induced hearing loss

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Efficacy of a Combined Drug Therapy for Ameliorating Noise-Induced Hearing Loss

by

Randi Lynn Luxmore

A Capstone Project
submitted in partial fulfillment of the
requirements for the degree of:

Doctor of Audiology

Washington University School of Medicine
Program in Audiology and Communication Sciences

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Approved by:
Jianxin Bao, Ph.D., Capstone Project Advisor
Brian Faddis, Ph.D., Second Reader

Abstract: Experiments investigated the median effective dose of antiepileptic drugs and synthetic glucocorticoids for the prevention and treatment of noise-induced hearing loss for C57BL/6J mice. We also tested the possible synergistic effects of combining drugs from the two drug families.
I would like to acknowledge the following individuals for their support throughout this project:

Dr. Jianxin Bao: For supporting and encouraging me throughout this process. Your vast knowledge and kind personality were both an inspiration to me.

Dr. Brian Faddis: For offering time and advice by serving as the second reader for this project.

Dr. Debin Lei: For teaching me the lab skills I needed for finishing this project, and for volunteering extra assistance without even being asked.

Michelle Hungerford: For helping with data collection and for being another avenue of support during this process.

My family: For always making education a priority, and for supporting me in every way so that I could work toward my goals.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>ABR</td>
<td>auditory brainstem response</td>
</tr>
<tr>
<td>CI</td>
<td>combination index</td>
</tr>
<tr>
<td>cm</td>
<td>centimeter</td>
</tr>
<tr>
<td>dB SPL</td>
<td>decibel sound pressure level</td>
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<td>GC</td>
<td>glucocorticoid</td>
</tr>
<tr>
<td>GR</td>
<td>glucocorticoid receptor</td>
</tr>
<tr>
<td>HPD</td>
<td>hearing protective device</td>
</tr>
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<td>IHC</td>
<td>inner hair cell</td>
</tr>
<tr>
<td>i.p.</td>
<td>intraperitoneal</td>
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<tr>
<td>kg</td>
<td>kilogram</td>
</tr>
<tr>
<td>kHz</td>
<td>kilohertz</td>
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<tr>
<td>mg</td>
<td>milligram</td>
</tr>
<tr>
<td>NIHL</td>
<td>noise-induced hearing loss</td>
</tr>
<tr>
<td>OBN</td>
<td>octave band of noise</td>
</tr>
<tr>
<td>OHC</td>
<td>outer hair cell</td>
</tr>
<tr>
<td>PTS</td>
<td>permanent threshold shift</td>
</tr>
<tr>
<td>sec</td>
<td>second</td>
</tr>
<tr>
<td>SGN</td>
<td>spiral ganglion neuron</td>
</tr>
<tr>
<td>SNHL</td>
<td>sensorineural hearing loss</td>
</tr>
<tr>
<td>TTS</td>
<td>temporary threshold shift</td>
</tr>
<tr>
<td>VGCC</td>
<td>voltage-gated calcium channel</td>
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Introduction

Noise-induced hearing loss (NIHL) is the single predominant health hazard posed by occupational and recreational settings (NIOSH, 2001). The incidence of NIHL has continued to grow in recent years partly due to growing popularity of portable music players with highly efficient headphones (Fligor and Cox, 2004; Serra et al., 2005). Although promising approaches have been identified for reducing NIHL mainly based on the free radical pathway (Lynch and Kil, 2005; Campbell et al., 2007; Kopke et al., 2007; Le Prell et al., 2007b), there are currently no effective pharmacologic agents in the clinical field to diminish permanent hearing loss. Development of an efficacious treatment has been hampered by the complex array of cellular and molecular pathways involved in NIHL. This project tests whether NIHL could be prevented by a synergistic pharmacologic intervention in multiple signaling pathways. Based on previous studies (Canlon et al., 2007; Shen et al., 2007), we have developed a two-drug combination therapy for NIHL with FDA-approved drugs from two different drug families: anti-epileptic drugs blocking T-type calcium channels and synthetic steroid drugs up-regulating the GC signaling pathway. The goal of this work was to explore this novel therapeutic direction for treating NIHL.

NIHL and its pathogenesis

After the initial noise exposure, auditory brainstem response (ABR) testing can typically detect two phases of hearing loss. These include a temporary threshold shift (TTS) that is most prominent in the first 24 hours, and an improved but still elevated permanent threshold shift (PTS) two to three weeks later (Clark, 1991; Quaranta et al., 1998; Nordmann et al., 2000). However, the dynamics of noise-induced damages and subsequent recovery are dependent on the intensity and duration of noise exposure (Wang et al., 2002; Harding and Bohne 2007). Three
distinct NIHL patterns have been well documented in CBA/CaJ mice (Wang et al., 2002). When the exposure is an 8-16 kHz octave-band of noise (OBN) at 94 dB SPL for two hours, there is an obvious TTS immediately post-exposure with a near complete recovery after two weeks (no significant PTS). From 100 to 112 dB SPL, the exposure causes a monotonic increase of both TTS and PTS, but partial recovery is observed (i.e., PTS is less than TTS). Above 116 dB SPL, the recovery of PTS is minimal possibly due to the regional rupturing of the reticular lamina. This noise level is defined as the “critical level” or the “inflection point” because the dramatic injury leads to the regional rupture of the reticular lamina and disruption of the endolymphatic compartment (Bohne, 1976, Wang et al., 2002; Harding and Bohne, 2007; Ohlemiller, 2008). The critical level is above 125-130 dB SPL for most animal models although it may be a little lower for mice, or when the exposure is temporally-skewed impact or impulse noise. In other animal models, similar changes are observed for these three NIHL patterns (e.g., Slepecky, 1986; Saunders et al., 1991; Lawner et al., 1997; Ohlemiller et al., 2000; Ohlemiller, 2008).

Histologically, above critical level, the most obvious pathological change is the rupture of the reticular lamina, detachment of the organ of Corti from the basilar membrane and degeneration of both inner and outer hair cells (IHCs and OHCs). Below critical level, injuries to the cochlea include: the organ of Corti (stereocilia disarray, small to moderate hair cell losses, and supporting cell damage), spiral ganglion neurons (SGNs; swelling of their terminals), stria vascularis (edema), and spiral ligament (loss of type IV fibrocytes).

Mechanical destruction and decreased blood flow contribute to NIHL in some instances (Spoendlin, 1971; Bohne, 1976; Ward et al., 1981; Quirk et al., 1991; Mulroy et al., 1998). One major mechanism underlying NIHL is the increase of mitochondrial free radical formation due to noise-induced intense metabolic activity in the cochlea (Lim and Melnick, 1971; Lynch and Kil,
The involvement of this pathway in NIHL is strongly supported mainly by three lines of evidence: First, a noise-induced increase of free radicals is observed in stria vascularis, OHCs, supporting cells of the organ of Corti, and SGNs (Yamane et al., 1995; Ohlemiller et al., 1999; Ohinata et al., 2000; Henderson et al., 2006), and this free radical insult can continue up to 14 days post-exposure (Yamashita et al., 2004). Second, the depletion of endogenous antioxidants and reduction of superoxide dismutase results in increased susceptibility to NIHL (Ohlemiller et al., 1999; 2000; McFadden et al., 2001). Third, an enhancement of antioxidants attenuates NIHL (Yamasoba et al., 1999; Ohinata et al., 2003; Duan et al., 2004; Lynch et al., 2004; Kramer et al., 2006). Due to these changes, it is not surprising that attempts to prevent NIHL by antioxidant agents have become the focus of much research in this field (Seidman et al., 1993; Hight et al.; 2003; McFadden et al., 2005; Yamashita et al., 2005; Bielefeld et al., 2007; Campbell et al., 2007; Kopke et al., 2007). Most of these interventions with single chemicals are only partially effective in preventing NIHL. Therefore, a few studies have started to intervene at multiple sites in the free radical pathway or in combinations with other pathways. Synergistic effects have been seen in some but not all of these studies (Yamasoba et al., 1999; Le Prell et al., 2007a; 2007b). These studies provide compelling evidence for the role of free radicals in NIHL, but they also suggest that other signaling mechanisms may contribute to NIHL.

**T-type calcium channels and glucocorticoids**

Among other main mechanisms contributing to NIHL such as the excitotoxic glutamate at the initial phase or cell death at the end phase (Puel et al., 2002; Le Prell et al., 2003; Guitton et al., 2004; Zine and Van De Water 2004), two new pathways have emerged: calcium and
glucocorticoid (GC) signaling pathways. Disturbance in calcium homeostasis has been suspected to contribute to trauma-induced neuronal injury (Nikenenko et al., 2005; Werling et al., 2007; Park et al., 2008). Calcium homeostasis in the cochlea can be regulated by several types of calcium channels, including voltage-gated calcium channels (VGCCs) (Rodrigues-Contreraz and Yamoah, 2001; Adamson et al., 2002; Fuchs 2002; Schnee and Ricci, 2003). VGCCs play a key role in calcium entry into neurons and control various calcium-dependent functions. These include neurotransmitter release, gene expression, synaptic plasticity, and neuronal excitability (Mattson 1990; Zipfel et al., 2000). VGCCs can be divided into two groups: high-voltage activated and low-voltage activated calcium channels (Igelmund et al., 1996; Lacinova et al., 2000; Perez-Reyes, 2003; Yunker and McEnery, 2003). The family of low-voltage activated, or T-type (Ca_v,3), calcium channels is comprised of three members (Ca_v,3.1, Ca_v,3.2, and Ca_v,3.3) based on their respective main pore-forming alpha subunits: a1G, a1H, and a1I (Perez-Reyes, 2003; Yunker and McEnery, 2003). The expression of a1G and a1I is found in the hair cells and supporting cells of the organ of Corti. A strong a1H and weak expression of the remaining two subunits are found in SGNs of the mouse cochlea (Shen et al., 2007). The same work has found that NIHL can be prevented by the administration of anticonvulsant drugs blocking T-type calcium channels either before or after the noise exposure. Inhibition of T-type calcium channels also protects neurons after stroke (Nikenenko et al., 2005). Thus, it is possible that pharmacological modulation of T-type calcium channels can prevent injury-induced alterations of calcium homeostasis, which may contribute to NIHL.

Another major molecular mechanism involved in NIHL is the GC signaling pathway. Synthetic GCs such as methylprednisolone are still used for clinical therapy of neural trauma such as spinal cord injury (Ahn and Fehlings, 2008; Xu et al., 2009). Synthetic GCs are also
used clinically to treat hearing loss in a variety of cochlear disorders such as autoimmune inner ear disease, tinnitus, and Menière’s disease (McCabe, 1979, Dodson and Sismanis, 2004; Dodson et al., 2004; MacArthur et al., 2008). Although no current reports exist on the clinical use of synthetic GCs for acoustic trauma, extensive evidence suggests an important role of GC pathways in NIHL. First, stressful preconditioning such as restraint, heat exposure, or even low-level sound in animal models has been found to be protective against NIHL (Paz et al., 2004; Wang and Liberman, 2002; Yoshida et al., 1999). Second, because the noise exposure itself is a stressful event, a pretreatment of blockers for GC signaling make animals more susceptible to NIHL (Tahera et al., 2006a). Third, synthetic GCs such as dexamethasone and methylprednisolone can protect against NIHL (Canlon et al., 2007; Henry, 1992; Lamm and Arnold, 1998; Sendowski et al., 2006; Tabuchi et al., 2006; Tahera et al., 2006b; Tahera et al., 2006c). Fourth, although GCs can bind to both GC receptors (GR) and minerocorticoid receptors, antagonists against minerocorticoid receptors have no effect on NIHL (Tahera et al., 2006a). Finally, a series of studies have systematically revealed the role of GR signaling pathways in NIHL (Canlon et al., 2007; Tahera et al., 2006b; Tahera et al., 2006c). In addition, the expression pattern of GR in the cochlea is known at both mRNA and protein levels. GR mRNA is detected in the cells of the spiral ligament, spiral limbus, and SGNs (ten Cate et al., 1993). GR immunoreactivity is also found in the organ of Corti (ten Cate et al., 1993; Zuo et al., 1995, Shimazaki et al., 2002). In mice, the adult GR expression pattern in the cochlea is achieved by postnatal day 14 (Erichsen et al., 1996), and can be up-regulated following acoustic stress (Tahera et al., 2006b).

Similar to the NIHL intervention methods based on the free radical pathway, current interventions based on synthetic GC drugs or anticonvulsants blocking T-type calcium channels
show limited success in preventing NIHL (Canlon et al., 2007; Shen et al., 2007). It must be noted that these two current interventions are from two completely different drug families, which most likely act on different molecular pathways underlying NIHL. The identification of specific drug combinations from these two drug families that may act in synergistic ways against NIHL is a logical next step for further study. Through this project, we validated this novel therapeutic approach to effectively prevent or treat NIHL.

**Methods**

**Animals**

All animal procedures were approved by the Animal Studies Committee at Washington University in St. Louis. The study included male and female C57BL/6J mice aged 2-6 months, purchased from Jackson Laboratories (Bar Harbor, ME, USA). All mice were housed two to five per cage in a noise-controlled environment on a 12h light/dark cycle with light onset at 6:00 a.m.

**Noise exposure**

Similar to the approaches described previously (Shen et al., 2007), noise exposures were performed in a foam-lined, double-walled soundproof room (Industrial Acoustics). The noise exposure apparatus consisted of a 21 x 21 x 11 cm wire cage mounted on a pedestal inserted into a B&K 3921 turntable. The cage was rotated at 1 revolution per 80 sec within a 42 x 42 cm metal bar frame. A Motorola KSN1020A piezo ceramic speaker (four total) was attached to each side of the frame. Opposing speakers were oriented not concentrically, but parallel to the cage and driven by independent channels of a Crown D150A power amplifier. Noise was generated by two General Radio 1310 generators and bandpassed at 4.0-45.0 kHz by Krohn-Hite 3550 filters. The overall noise level was measured at the center of the cage using a B&K 4135 ¼ inch
microphone in a combination with a B&K 2231 sound level meter set at broadband (0.2 Hz-70 kHz). Mice were exposed in pairs to white noise at 110 dB SPL for 30 minutes.

**Drug administration**

Mice were randomly assigned to either experimental or control groups. For the prevention protocol, the experimental mice were given the drugs in an intraperitoneal (i.p.) injection and the control mice were i.p. injected with normal saline. The drugs were injected 2 hours before noise exposure.

![Figure 1: Example of the prevention protocol used in this study](image)

For the treatment protocol, the experimental mice were i.p. injected with the different drugs and the control mice were i.p. injected with normal saline 24 hours after noise exposure. An additional treatment protocol was performed in which the drugs were orally fed in a 1% sucrose solution, and the control mice were fed with the 1% sucrose solution only. The drug administrations began approximately 24 hours post noise exposure and were monitored for two weeks in the drinking water.

![Figure 2: Example of the treatment protocol used in this study](image)
Auditory brainstem recording

The mouse cochlea typically responds to frequencies ranging from 2-100 kHz. The most sensitive region of the audiogram is roughly 5-40 kHz. To cover this range, we tested at 5, 10, 20, 28.3, and 40 kHz. The “near field” sound stimulation and calibration were used in which the speaker was near the ear (7 cm) within the range where the sound field was approximately homogeneous within an imaginary cylinder surrounding the ear. To make sure sound stimuli were constant from animal to animal, a B&K 4135 ¼ inch microphone was placed where the mouse ear would normally be and calibrated before the experiment. Prior to testing, all mice were anesthetized with pentobarbital (60 mg/kg, i.p.) and given atropine sulfate (0.5 mg/kg, i.p.) to reduce respiratory distress. Core temperature was maintained at 37 +/- 1 °C using a thermostatically controlled heating pad in conjunction with a rectal probe (Yellow Springs Instruments Model 73A). Platinum needle electrodes (Grass) was inserted subcutaneously just behind the right ear (active), and at the vertex (reference), and in the back (ground). Electrodes were led to a Grass P15 differential amplifier (100-10,000Hz, x100), then to a custom amplifier providing another x1,000 gain, finally digitized at 30 kHz using a Cambridge Electronic Design Micro1401 in conjunction with SIGNAL™ and custom signal averaging software operating on a 120 MHz Pentium PC. Sinewave stimuli generated by a Wavetek Model 148 oscillator were shaped by a custom electronic switch to 5 ms total duration, including 1 ms rise/fall times. The stimulus was amplified by a Crown D150A power amplifier and output to a KSN1020A piezo ceramic speaker. Toneburst stimuli at each frequency and level were presented 1,000 times at 20/sec. The minimum sound pressure level required for a response (short-latency negative wave) was determined at selected frequencies, using a 5 dB minimum step size.
Results

Because this was the first study attempting to establish the pharmacokinetics of these drugs for protection from NIHL, we did not know whether first-order or higher-order dynamics existed in the dose-effect curve for each drug. Thus, we began our study with the focus on the median effective dose ($ED_{50}$) determination by using the median-effect equation (Chou, 2006). The median effect equation is the general equation for the dose-effect relationship derived from the mass-action law principle that takes into account both the potency and the shape of the dose-effect curve (Chou, 2006). The $ED_{50}$ of a drug is the amount of drug that produces a response in 50% of the subjects taking it. Two steps decided the dosage range: (1) to obtain the known $ED_{50}$ based on previous studies, and (2) to expand the dosage to determine the $ED_{50}$ against NIHL.

The ABR shift curves for corticosteroid drugs, at multiple dosages are present in Figure 1, and the ABR shift curves for anti-epileptic drugs are present in Figure 2.

Figure 3: NIHL prevention by the synthetic corticosteroid drugs. (A) ABR thresholds among the control and different dosages of methylprednisolone ($n=8$ for each group); (B) ABR thresholds among the control and different dosages of dexamethasone ($n=8$ for each group).
After these observations, we entered these data into the CompuSyn software (ComboSyn, Inc) to calculate ED50s based on the median-effect equation. The ED50s to prevent NIHL for drugs from two different drug families were: methylprednisolone (525 mg/kg), dexamethasone (39.4 mg/kg), and zonisamide (125 mg/kg). Because the unpredictable nature of ethosuximide (Figure 2A), no ED50 could be obtained for this drug.

Because we only obtained the ED50 for zonisamide in the antiepileptic family, the combination of zonisamide with either methylprednisolone or dexamethasone was tested at different dosages to determine possible synergic effect between these combinations. A combination of methylprednisolone and zonisamide at lower dosages (8 and 60 mg/kg respectively, or their ED10 values) was found to effectively prevent NIHL (Figure 5). With the same CompuSyn software, a synergic effect was found for these two drugs to prevent NIHL based on the value of the combination index (CI), which was equal to 0.97.
Figure 5: NIHL prevention by a drug combination of methylprednisolone and zonisamide at their low dosages. ABR thresholds were about 10 dB lower across four frequencies between the control (blue line) and treated mice (red line, n=6 for each group). A synergistic effect was found due to the fact of CI < 1.

Similarly, the ED_{50}s to treat NIHL 24 hours after the noise exposure were also determined for all four drugs from the same two drug families (Figure 6). The exact ED_{50}s were: methylprednisolone (95.6 mg/kg), dexamethasone (96.3 mg/kg), zonisamide (2543 mg/kg), and ethosuximide (243 mg/kg). However, little evidence existed for possible synergistic effects to treat NIHL by i.p. injections with these two families of drugs. Interestingly, by oral administration for two weeks, we did find a considerable effect to treat NIHL by the two-drug treatment (Figure 6E). Thus, our data provided important preclinical drug information to prevent and treat NIHL.
Figure 6: NIHL treatment by glucocorticoid and antiepileptic drugs. (A) ABR thresholds among the control and different dosages of methylprednisolone ($n=8$ for each group), (B) ABR thresholds among the control and different dosages of dexamethasone ($n=9$ for each group); (C) ABR thresholds among the control and different dosages of ethosuximide ($n=8$ for each group); (D) ABR thresholds among the control and different dosages of zonisamide ($n=8$ for each group); and (E) ABR thresholds between the control and a combination of methylprednisolone and ethosuximide fed in the drinking water over 24 hours after the noise exposures for two weeks ($n=4$ for each group)
Discussion

NIHL is a major health issue without effective medication, mainly due to the multiple factors contributing to this complex disease. Based on previous studies in the advisor’s laboratory, we have carried out the first detailed pharmacodynamic study examining a combination therapy against NIHL. The first part of the study concentrated on the possible prevention of NIHL, while the second part looked at a possible treatment. ED50s against NIHL for drugs from two different families (two drugs per family) were derived based on ABR testing, and a synergistic effect for one drug combination was discovered to prevent NIHL.

NIHL Prevention

Various studies have found that synthetic GCs such as methylprednisolone and dexamethasone can protect against NIHL. This effect is in conjunction with its biologic function of promoting neuronal adaptation and survival (McEwen, 2008). The advisor’s lab has previously found that 5 mg/kg of methylprednisolone injected two hours before noise would reduce NIHL in the mouse model. In addition, significant preservation of hair cells and SGNs were found as compared to the control group. Drugs blocking T-type calcium channels were also found to partially prevent NIHL (Shen et al., 2007). Therefore, it was not completely surprising for this study to obtain different ED50 values for each drug from these two families.

However, it is considerable that we discovered a synergistic effect against NIHL with a combination of methylprednisolone and zonisamide. This was based on the fact that the CI = 0.97. The CI is beneficial because it creates a quantitative measure of the degree of drug interaction in terms of synergistic (CI<1), antagonistic (CI>1), and additive (CI=1) effects (Chou, 2010). Therefore, the effects of methylprednisolone and zonisamide together were greater than what would be expected when adding each of their individual effects together.
Based on this finding, drugs blocking T-type calcium channels and synthetic glucocorticoids could be part of a promising new avenue of prevention.

Although these results are very encouraging, they are not without limits. First, these results were obtained in a controlled laboratory environment with genetically identical animals. Thus, these results need to be explored further in other animal models. If these results look promising, then clinical trials with humans can begin. Another consideration is the fact that many times, noise exposure is unexpected. Therefore, any compounds that prevent NIHL will be unusable in these situations. This will be true especially for those in military operations. Impulse noise is a huge concern for the military, combined with the fact that many soldiers choose not to consistently wear hearing protective devices (HPDs) despite hearing conservation programs stressing their usage. A therapy that can treat NIHL will benefit this population greatly.

**NIHL Treatment**

The ED$_{50}$s for the treatment of NIHL were found for all four drugs as well. Interestingly, these values were quite different than those for the prevention of NIHL. With the exception of methylprednisolone, all of the drugs had much higher ED$_{50}$s for the treatment of NIHL. This difference strongly suggests an optimal therapeutic time window for NIHL. In our NIHL prevention diagram, each drug should have its effect most likely after the noise exposure due to their long half-life (Table 1), although all drugs were applied two hours before the noise exposure. Half-life is defined as the time required for half of the quantity of a drug to be metabolized in a living organism. For example, it would take around 50-70 hours to lose half of the potency of zonisamide after the injection. Therefore, its effects against NIHL before the noise exposure could only account for 2/70 (about 3%). Because of this we found that drugs were
more effective against NIHL if they were injected two hours before the noise exposure instead of 24 hours after the noise exposure. It strongly suggested that the ideal time window for these drugs within the first 24 hours after the noise exposure.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Human Dosage (mg/kg)</th>
<th>ED50 (mg/kg)</th>
<th>Half-life (hours)</th>
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<tr>
<td>Methylprednisolone</td>
<td>4</td>
<td>30-35</td>
<td>18-36</td>
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<tr>
<td>Dexamethasone</td>
<td>0.75</td>
<td>0.13</td>
<td>36-54</td>
</tr>
<tr>
<td>Ethosuximide (Zarontin)</td>
<td>250</td>
<td>130</td>
<td>30-60</td>
</tr>
<tr>
<td>Zonisamide (Zonegran)</td>
<td>100-600</td>
<td>40</td>
<td>50-70</td>
</tr>
</tbody>
</table>

Table 1: The human dosages (mg/kg), ED50 values (mg/kg) for humans, and the half-life (hours) for the four drugs used in this study

In addition, this study has shown that reduction of noise induced threshold shifts can occur from all four of the drugs that were used. It was interesting to note that no synergistic effects in the NIHL treatment were obtained from any drug combinations using an i.p. injection approach. Yet, a marked effect was found between methylprednisolone and ethosuximide when they were orally administered for two weeks after noise exposure. It is unknown why a difference in administration techniques can result in a different effect on ABR thresholds. This topic would need to be addressed in future research. Using an oral administration approach could be more efficient and practical for human use. Promoting these drugs in a supplement form would allow people to ingest the drugs without coming to a professional for an injection. The two-week time course, however, may be more of an issue outside of a lab setting. Some could forget to take the dosage every day, or it could be perceived as too cumbersome and the treatment could be rejected.
Future Research

For both the prevention and treatment protocols, further research is needed. Future studies would need to investigate the most effective dosages of each drug in combination with another. The time course and method of drug administration both need to be investigated further as well.

Conclusion

In this study, we set out to investigate the effects that FDA approved drugs from two different families could have on ameliorating NIHL. These two families, T-type calcium channel blockers and synthetic glucocorticoids, affect two different pathways known to be involved in NIHL. No such study has been attempted with these compounds before. This study had two phases: one investigating the prevention of NIHL, and one regarding the treatment of NIHL. We found that the administration of each of these drugs before noise exposure has an effect on PTS. In addition, the low dosage combination of two of these compounds can also have an effect by reducing PTS compared to controls. The second phase illustrated that each of these drugs also has a positive effect on PTS when administered 24 hours after noise exposure. However, this effect is markedly less than that of the prevention protocol. A synergism between two of the drugs was found when they were orally administered for two weeks after noise exposure. This novel investigation demonstrated that pharmaceutical intervention before or after noise exposure could ameliorate some effects of NIHL.
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superoxide dismutase gene (Sod1) increases susceptibility to noise-induced hearing loss.


