PHARMACEUTICAL INTERVENTIONS FOR HEARING LOSS (PIHL)

Newsletter – Winter 2018/Edition 7

CONTENTS

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FOREWORD

Since the last Pharmaceutical Interventions for Hearing Loss (PIHL) newsletter was published in autumn 2016, much change has occurred in the Department of Defense (DoD) Hearing Center of Excellence (HCE) and the PIHL Group. The HCE obtained new leadership and transitioned into the Defense Health Agency (DHA). Meanwhile, the PIHL Group underwent a reorganization of its committees.

The HCE saw the departure of Colonel (Ret) Dr. Mark Packer, and the entrance of Colonel (Dr.) LaKeisha Henry, for service as the HCE's Division Chief. Colonel Henry has been stationed at Joint Base San Antonio-Lackland, Texas to lead the HCE through the execution of its congressionally-directed mission. She is an otolaryngologist within the San Antonio Military Health System and is actively involved as a teaching faculty member for several organizations. Colonel Henry most recently served as the 59th Medical Group's Otolaryngology Master Clinician and has previously served as a Squadron Commander in addition to other leadership roles during her numerous clinical assignments both in the U.S. and overseas. In addition to the roles previously outlined, Colonel Henry serves as the Otolaryngology Consultant to the Air Force Surgeon General. More about Colonel Henry can be found on the HCE's website: https://hearing.health.mil/About-HCE/Leadership/HCE-Leadership.

The DHA is an integrated Combat Support Agency of the joint medical services from the Army, Navy, and Air Force that supports the delivery of integrated, affordable, and high quality health services to Military Health System (MHS) beneficiaries. Among its varied responsibilities, the DHA enables rapid adoption of proven practices, helps reduce unwanted variation, and improves the coordination of care across time and treatment venues. The HCE now resides under the DHA Research and Development (J-9) Directorate. More about the DHA can be found on its website: https://health.mil/dha.

The PIHL Group brings together experts across the globe from the DoD, Department of Veterans Affairs (VA), academia, and industry. The PIHL Group is a member-driven organization whose subject matter experts come together to discuss, develop, and disseminate knowledge products. This newsletter, the seventh in the series, is one such product. Other products have included special editions of peer-reviewed journals (Otology & Neurotology, September 2016;

CONGRESSIONALLY – DIRECTED HCE MISSION STATEMENT

To optimize operational effectiveness, heighten medical readiness, and enhance quality of life through collaborative leadership and advocacy for hearing and balance health initiatives.

DHA J-9 MISSION STATEMENT

J-9 leads the discovery, development, and delivery of enhanced pathways to military health and readiness.

Hearing Research, June 2017; and both the International Journal of Audiology and Frontiers in Cellular Neuroscience, which are expected in early 2018, as will be highlighted further in this newsletter). The PIHL Group has also hosted symposia meetings and an Association for Research in Otolaryngology (ARO) workshop in 2016. Much of this work has been performed by the committees. The original formation of the group included eight committees: 1) DoD Functional Requirements, 2) Temporary Threshold Shift (TTS) vs. Permanent Threshold Shift (PTS), 3) Sound Exposures, 4) Clinical Trial Testing Guidelines, 5) Animal Models, 6) Delivery Methods, 7) Statistical Considerations, and 8) Genomic Considerations. These were honed down to three committees and a fourth committee was added: 1) Clinical Trials, 2) Sound Exposures, 3) Animal Models, and 4) Ototoxicity. During the summer of 2017, the Animal Models, Clinical Trials, and Sound Exposures Committees were re-organized into the Noise Exposures Committee, the Drugs Committee, and the Measures Committee. The Ototoxicity Committee remains as well. This newsletter will provide introductions to the newly-formed Noise Exposures and Drugs Committees while focusing on the contributions of the Ototoxicity Committee.

I thank all of the members of the PIHL Group who contributed to the accomplishments mentioned here and highlighted later. Your efforts deserve a round of applause!

With much respect,

Kelly Watts, AuD
Co-chair of the Ototoxicity Committee for the PIHL Group
Northeast Regional Research Administrator for the HCE
Research Audiologist at the Naval Submarine Medical Research Laboratory (NSMRL), Groton, CT
Contractor for zCore Business Solutions

INTRODUCTION TO THE PIHL COMMITTEES

Noise Committee

The PIHL Noise Committee, under the leadership of University ot Texas (UT) Dallas's Dr. Colleen Le Prell and the HCE's Mr. J.R. Stefanson, is developing a series of white papers with the overarching goal of describing real-world noise hazards and patterns of noise-induced injury in as much detail as possible, including careful discussion of sources of variability, so that the most appropriate animal models can be selected when a drug is developed for potential application. Comprehensive reviews of the effects of different types of noise exposures are planned, with careful attention to differences across species. The need for this data is driven by increasing awareness that otoprotective drugs are not developed in a vacuum; they are developed for specific populations and markets. Right now, animal models have not been characterized in enough detail to allow the selection of the most appropriate pre-clinical test models. This translational framework will be emphasized as papers are prepared.
Topics areas are broadly defined as follows:

- Human exposures and associated hearing loss profiles
- Factors influencing variability in TTS/PTS
- Animal models used to identify effects of noise on hearing

This committee is seeking volunteers willing to contribute to initial white paper development this spring. The group anticipates the preparation of full-length manuscripts during Summer 2018, with an October deadline for articles.
Interested individuals are encouraged to contact J.R. @ earl.w.stefanson.ctr@mail.mil or Colleen @ colleen.leprell@utdallas.edu.
Membership in this committee is open to all interested individuals.

Colleen Le Prell, PhD
Co-chair of the Noise Committee for the PIHL Group
2017-2018 President of the National Hearing Conservation Association (NHCA)
Emily and Phil Schepps Professor of Hearing Science, University of Texas at Dallas
Head of the Doctor of Audiology Program, University of Texas at Dallas

J.R. Stefanson
Co-chair of the Noise Committee for the PIHL Group
Southeast Regional Research Administrator for the HCE
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Drugs Committee

We want to welcome to the PIHL community the new Drugs Committee. This group meets the last Friday of the month at 1200 EST/0900 PST. The focus of the Drug Committee is to support drug development efforts in industry and academia by summarizing and disseminating knowledge related to the current and emerging pharmaceutical market targeting hearing and vestibular disorders, making original contributions to the literature (e.g., reviews), and fostering collaboration and networking among researchers and developers. The committee is new and the objectives are still taking shape; they include:

1) Maintain and publish a *Drugs Reference Table* that summarizes the current state of the science,
2) Identify optimal dosing regimens based on the information gathered from Industry, Academia, and published resources,
3) Disseminate "Lessons Learned" from failures in clinical testing (e.g., routes, timing, cellular targets),
4) Increase networking among researchers from industry and academia around the world.

We would be delighted to have fellow researchers, developers, and other stakeholders join our efforts. If you are interested, we invite you to attend the monthly meetings or reach out to the group coordinators Dr. Kate Marshall at Kathryn.e.marshall2.ctr@mail.mil and Dr. Julieta Scalo at j.scalo@posteo.net.

Kate Marshall, PhD
Co-chair of the Drugs Committee for the PIHL Group
Northwest Regional Research Administrator for the HCE
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Co-chair of the Drugs Committee for the PIHL Group
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Ototoxicity Committee

The PIHL Group formed an Ototoxicity Committee as a platform for discussions of both basic and clinical science involved in ototoxicity, including the related topics of prevention, repair, and mitigation. As a starting point, this committee defined ototoxicity as damage to auditory or vestibular structures or functions as the result of exposure to certain pharmaceuticals, chemicals, and/or ionizing radiation. In this context, otoprotection primarily involves

pharmaceutical strategies but may also comprise other strategies, including the need to reduce other potentiating exposures. After a discussion of ototoxicity monitoring protocols and, in particular, their apparent lack of standardization across clinics who perform ototoxicity monitoring, an Ototoxicity Monitoring Subcommittee was formed. One of the current efforts from this Subcommittee is to develop a survey that when utilized will provide a better understanding of current practices in ototoxicity monitoring. This committee focuses primarily on clinical issues and solutions to ototoxicity caused by pharmaceuticals and/or ionizing radiation. Although we know that occupational exposure to chemical solvents, metals, and asphyxiants can also cause damage to the auditory system, especially when contact is compounded with exposure to hazardous noise (American Academy of Audiology, 2009; Hecht, et al., 2017), this has yet to become a formalized area of interest for this subcommittee.

The Ototoxicity Committee is always open to new members and the ideas that they bring. Our roster currently represents a variety of clinical and research interests from the DoD, VA, National Instituties of Health (NIH), academia, and industry throughout the world. Our subject matter experts have provided valuable input to two forthcoming special editions, the details of which will be provided in the following articles by Drs. Amy Boudin-George, Carmen Brewer, and Peter Steyger. If you are interested in our discussions or contributing to the next publication, we invite you to attend the monthly teleconferences or reach out to Dr. Kelly Watts, the primary administrator for this committee, at Kelly.L.Watts3.ctr@mail.mil.

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CLINICAL MONITORING OF OTOTOXICITY – STRATEGIES FOR SUCCESS AND A LOOK INTO THE FUTURE

The supplemental edition of the International Journal of Audiology (IJA), "Ototoxicity – Special Topics in Clinical Monitoring," is nearing completion. It was proposed with the intent to be one aspect of the solution to barriers that exist in successful implementation of ototoxicity monitoring protocols (OMPs). There are 13 articles prepared for this supplemental edition that address topics regarding ototoxic medications, current considerations for OMPs, barriers to success and strategies to overcome them, as well as where the future will take us in the prevention and mitigation of ototoxicity-induced loss of auditory and vestibular function.

The audiology community has long known that monitoring for medication-induced ototoxicity is helpful in patients' auditory and vestibular outcomes. OMPs serve to inform the patient, lay and medical caregivers, pharmaceutical companies, and government monitoring agencies about the ototoxic effects of therapeutic regimens. On an individual level, an OMP helps to ensure that patients and their families are informed about the risks and symptoms of ototoxicity. While hearing changes may be one of several adverse effects of a therapeutic treatment, understanding the potential for ototoxicity contributes to informed decision-making regarding management strategies. Early identification of hearing loss allows audiologists and medical teams to mitigate the effects of ototoxicity by reducing exposure, if possible, and implementing treatment and communication strategies early on. Though guidance exists to inform monitoring protocols (e.g., what tests to perform and what constitutes a significant hearing change; American Speech-Language Hearin Association, ASHA, 2004; AAA, 2009) gaps in care may still exist due to difficulties encountered in program development and implementation. The Ototoxicity Monitoring Subcommittee of the PIHL Group postulated that the lack of successful, comprehensive OMPs may be attributable, at least in part, to lack of guidance regarding the "how tos" related to development of program logistics, promotion of the value and importance of audiologic monitoring to stakeholders, and communication of significant findings and recommendations to the patient and patient care team.

Interviews with four treatment care providers (one oncologist and three pulmonologists) in the United States shed light on the physician viewpoint regarding ototoxicity monitoring in Garinis, et al. (e-published 2017). Although there is an understanding that ototoxicity is a potential problem and monitoring is important, the approaches to ototoxicity monitoring vary by provider and institution. Similarly, in the United Kingdom (UK), questionnaire responses from healthcare providers in the UK National Health Service indicate that referral methods, testing protocols, and post-treatment follow-up vary widely by treatment center and provider (Maru and Al-Malky, in review). These results

highlight the need for national and international protocols for the management and monitoring of ototoxicity.

Barriers to implementation of adult OMPs exist even for some of the premier programs in the private sector, VA, and DoD clinics. Audiology participation in oncology multi-disciplinary team clinics, referrals generated by the pharmacy, and dedicated appointment slots, personnel, and rooms can mitigate some of these barriers (Konrad-Martin, et al., e-published 2017). Further solutions can be found in the use of new technology in clinical settings. By making test equipment portable and boothless via methods such as tablet-based testing, patients can be easily and reliably tested at their bedside, reducing burden on patients and providers, while freeing up space in the audiology clinic (Brungart et al., e-published 2017).

The importance of and approach to ototoxicity monitoring in infants and children is addressed by two articles in the supplemental edition. Brooks and Knight remind us that the risk for cisplatin ototoxicity in pediatric patients is higher than that of adults. This is of considerable concern in infants and children for who even a slight hearing loss can have a detrimental impact on speech and language development, literacy, and educational success. Pediatric ototoxicity monitoring approaches vary with patient age, attention, and ability to complete various examinations, making it important that a priori strategies are in place to ensure that the most important audiometric information is obtained first (Brooks & Knight: e-published, 2017). Whereas cisplatin is the most commonly used ototoxic drug in children, in the neonatal population, aminoglycosides are the most often used. Their effect on hearing may be exacerbated by concurrent medications, inflammatory status, genetics, and noise levels in the Neonatal Intensive Care Unit. There are no widely accepted protocols for monitoring ototoxicity in neonates. Subsequently, newborn hearing screening methods, which are designed to focus on the speech frequencies and not the higher frequencies, are the most commonly used approach for ototoxicity monitoring in neonates. Garinis et al. bring this current limitation to our attention (Garinis et al., e-published 2017).

There are several scales by which ototoxicity can be classified for the purpose of clinical trials and clinical ototoxicity monitoring protocols. These grading scales differ in many aspects of how hearing loss is defined or deemed actionable, age range covered, and testing requirements. Knowledge of the types of scales and their applicability to the clinician's patient populations is imperative in being able to select the most suitable scale. Similarly, for those participating in clinical trials, fully understanding the requirements of an ototoxicity grading scale will ensure consistent and accurate collection and interpretation of hearing data shared with researchers, regulatory agencies and other stakeholders (King and Brewer, e-published 2017).

The incidence of vestibulotoxicity is often overlooked in OMPs, and vestibular issues can be difficult to quantify, as the typical battery of tests may be complex and require more attention and endurance than an ailing patient

may have. Vestibulotoxicity evaluation methods may include both subjective questionnaires and objective bedside and formal laboratory tests. When used in concert for baseline metrics, these tests can be sensitive to changes in vestibular function regardless of the patient's ability to return to the clinic or perform an entire battery of tests (Handelsman, in review).

The existing literature on treatment modalities for head and neck squamous cell carcinoma indicates the treatment for this type of tumor typically includes cisplatin and radiation therapy, with possible resection of the tumor. Due to the proximity of the radiation to the cochlea, middle ear, and Eustachian tube, standard protocols for cisplatin chemotherapy and radiation, in combination, may have more ototoxic effects than either in isolation. Other treatment paradigms with more frequent, lower doses of cisplatin, other medications, or newer therapeutic delivery models may reduce ototoxic effects, but more research is needed in this area (Schmitt & Page, e-published 2017).

Studies on the prevention of ototoxicity-induced hearing loss indicate that, particularly in animal models, concurrent administration of vitamins and antioxidants for management of intracochlear oxidative stress has been successful. Other methods being studied are steroids, salicylates, and a reduction in the required dosage of cisplatin by concurrently administering agents that sensitize tumor cells to the therapeutic drug (Hammill and Campbell, in review). This review article suggests that the prevention and mitigation of ototoxicity-induced hearing loss in humans may be on the horizon. Proof of ototoxic protection will require clinical trials. As we move in this direction, patient recruitment for clinical trials will be a critical consideration. Sanchez et al. (in review) examined the success of various recruitment methods for concurrent clinical trials of pharmaceutical interventions for hearing related disorders in the US and UK. The most efficient method in both locations was through printed material in hearing-related publications for both patients and providers.

We hope this effort provides a starting point for the implementation and enhancement of clinical monitoring programs for ototoxicity and provides some forward-thinking for what lies ahead in our profession. The complete open-access journal will not be published by the time of this Newsletter's release, but more than half of the articles have been electronically released and can be found on the IJA website (http://www.tandfonline.com/action/showAxaArticles?journalCode=iija20). We are grateful for the valuable contributions of the many authors and reviewers. In addition, we thank the DoD HCE for sponsoring this supplemental edition.

Amy Boudin-George, AuD
DoD HCE

Carmen Brewer, PhD
National Institute on Deafness and Other Communication Disorders

~Associate Editors, Supplemental Edition of the IJA, "Ototoxicity – Special Topics in Clinical Monitoring"

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A CASE STUDY IN OTOTOXICITY: CLEAR COMMUNICATION IN CLINICAL CARE

On 31 October 2017, two urgent consultation requests were sent from the Infectious Disease department to the Audiology department within a VA Medical Center, which triggered a series of events. The requests were to establish baseline cochlear and vestibular function prior to treatment with tobramycin. The following will provide details on this case.

Aminoglycoside ototoxicity

Aminoglycoside antibiotics are known ototoxic agents and the risks for hearing loss and vestibular dysfunction should be taken into consideration when determining a treatment plan including these drugs (Leis et al., 2017). The referred patient in this case was to be treated with the aminoglycoside tobramycin. Although there is some controversy to the ranking, tobramycin can be considered as the third most vestibulotoxic aminoglycoside behind streptomycin and gentamycin (Govaerts et al., 1990).

The expression of ototoxicity may depend on the quantity and frequency of the treatment dose, concomitant use of other pharmaceuticals (especially loop diuretics, e.g. furosemide) (Aran, Erre, Lima De Costa, Debbarh, & Dulon, 1999), and other more intrinsic factors (Guthrie, 2008; Brummett, Fox, Jacobs, Kempton, Stokes, & Richmond, 1990). The dosing schedule and patient-specific factors in this case are described in a later section. The biological mechanisms of aminoglycoside-induced ototoxicity are complex and are thought to involve the formation of reactive oxygen species (ROS), sensory cell death through apoptosis, and synaptopathy (Guthrie et al., 2008; Chen et. al., 2008; Lesniak, Pecoraro, & Schacht, 2005). A review of the mechanisms involved in the cochleotoxicity of aminoglycosides can be found in Jiang, Karasawa, and Steyger (2017). New evidence shows that non-apoptotic effects contribute to aminoglycoside vestibulotoxicity, specifically: decreases in stimulus-evoked afferent discharge modulation, retraction of afferent calyces, and damage to afferent dendrites (Sultemeier & Hoffman, 2017). Additionally, Takumida & Anniko (2000, 2001) found that in guinea pigs, gentamycin exposure resulted in excess production of nitric oxide (NO) due to overstimulation of NMDA receptors. Using a fluorescence microscope, they determined that the vestibular hair cells were absorbing the excess NO and that this was a possible mechanism of vestibulotoxicity.

Human studies examining the effects of aminoglycosides on cochlear and vestibular function have focused on at risk populations, such as patients with Cystic Fibrosis (CF). CF is an autosomal recessive genetic disorder that impacts respiratory function, which results in a higher incidence of infections of the respiratory system (frequently *Pseudomonas aeruginosa*) (Pauna, Monsanto, Kurata, Paparella, & Cureoglu, 2017). As a result of this, CF patients are repeatedly prescribed long-term courses of antibiotics; tobramycin is frequently the drug of choice used to treat these infections (Scheenstra, Rijntjes, Tavy, Kingma, & Heijerman, 2009; Doring, et al., 2000). Histologic studies have been completed looking at temporal bones of patients who had a diagnosis of CF (Pauna et al., 2017). In their 2017 study, Pauna et al. examined 12 temporal bones from patients who had a diagnosis of CF; of these, 10 had been exposed to at least one aminoglycoside antibiotic. The temporal bones of the CF group were found to have: reduced density of type I and II hair cells, a reduction in the number of dark cells, and a reduction in the number of transitional cells when compared to the control group (Pauna et al., 2017). The results of the Pauna et al (2017) study support the hypothesis that damage to structures of the vestibular system by aminoglycoside antibiotic is responsible for clinical symptoms of vertigo/imbalance. Scheenstra et al. (2009) found a prevalence of 30.4% (7 out of 23 participants) for peripheral vestibular dysfunction in their study with the vast majority, 5 out of 7 or 71.4%, of those with symptoms exhibited bilateral dysfunction. Peripheral vestibular hypofunction was determined by an abnormal ENG.

Given the finding of Scheenstra et al. (2009) that patient report of symptoms via a questionnaire was a poor predictor of changes in vestibular function, the need for an objective monitoring protocol of vestibulotoxicity with aminoglycoside use is indicated. This lack of patient report of symptoms may be due to a more gradual onset of vestibulotoxicity with aminoglycosides compared to more acute infarcts (e.g. labyrinthitis). Scheenstra et al (2009) recommended the use of electronystagmography (ENG) for monitoring vestibular function but acknowledged this is controversial due to the many variables that can impact the test: patient instruction / understanding of instruction, room conditions, experience level of examiner, quality of irrigation, consistent positioning, etc.). The appropriateness of using this test for monitoring will be discussed further in a subsequent section of this paper.

There are established protocols for monitoring of cochleotoxicity in aminoglycoside and other ototoxic medication treatments (Konrad-Martin et al, 2017; ASHA, 1994; AAA, 2009) but the same is not true for monitoring vestibular function; although, efforts are ongoing to establish vestibular protocols (Van

Hecke, Van Rompaey, Wuyts, Leyssens, & Maes, 2017; Handelsman, in press). As pointed out in Sultemeier & Hoffman (2017), an understanding of the mechanisms by which aminoglycosides damage the vestibular apparatus is critical to developing monitoring protocols for early identification of peripheral vestibular dysfunction. Damage to vestibular structures in aminoglycoside ototoxicity is typically bilateral in nature, which results in symptoms that are not always recognized as being linked to vestibular function (e.g. disequilibrium, postural instability and oscillopsia (van Hecke et al., 2017; Scheenstra et al., 2009). In many cases, these symptoms may be mistakenly attributed to an underlying condition or masked by the fact that a patient is bedridden. Additionally, loss of vestibular function can be masked by sensory substitution, where vision and proprioception help compensate for the loss of vestibular function in certain situations (van de Berg, van Tilburg, & Kingma, 2015). Unlike hearing loss, the vestibular loss seen with aminoglycoside treatment may be temporary and function sometimes improves after treatment is ceased (Guthrie, 2008; Black, Gianna-Poulin, & Pesznecker, 2001). Early detection through monitoring can help prevent permanent damage given the findings of Aran et al. (1999) where, at least in guinea pigs, the effects of an acute exposure to an aminoglycoside (gentamycin) on cochlear function were reversible. Black et al (2001) found horizontal canal vestibulo-ocular reflex (VOR) improved in most participants. The participants were all recovering from serious systemic illness and did not participate in any vestibular rehabilitation therapy (VRT). Recovery of function took up to one year post cessation of treatment (Black et al., 2001; De Waele et al., 2002). These are interesting findings given that gentamycin is often used for chemical ablation of the vestibular organs in severe Meniere's cases.

Recovery of vestibular function (measured with caloric testing) has been seen in patients treated with an intratympanic injection of gentamycin for intractable vertigo most commonly due to Meniere's disease, which in these cases would not be a desirable outcome unlike in therapeutic use of aminoglycosides. De Waele (2002) study saw this recovery occurring 12 months post injection and presumed that this recovery of function was due to hair cell regeneration. A more recent study (Sultemeier & Hoffman, 2017) suggests that there could also be regeneration of non-apoptotic effects of gentamycin behind these improvements in function. The longest post exposure measurements in the Sultemeier & Hoffman (2017) study was 6 months which they acknowledge is insufficient to show recovery based on the De Waele et al. (2002) findings, therefore Sultemeier & Hoffman (2017) suggest that the findings of De Waele et al. (2002) may indicate recovery of function for non-apoptotic

lesions in addition to hair cell regeneration. It should be noted, however, that the aforementioned studies showing recovery of vestibular function were conducted with gentamycin, streptomycin, or dihydrostreptomycin rather than tobramycin.

Case Study

The patient is a 68 year old white male US Navy Veteran who presented to the Audiology department on 31 October 2017, with urgent consultation requests for hearing and vestibular evaluations in order to establish baseline status immediately prior to starting on long term intravenous aminoglycoside antibiotic (tobramycin) treatment. This treatment was indicated due to cutaneous infectious lesions on his left lower leg which had not responded to other (oral) antibiotics. The bacterial agent causing the lesions was identified as *Mycobacterium chelonae* (M. chelonae), a non-tuberculosis mycobacterium (NTM). M. chelonae is ubiquitous in the environment and resistant to many cleaning agents (e.g. chlorine and glutaraldehyde) (Svetlikova, Skovierova, Niederweis, Gallard, McDonnell, & Jackson, 2009). Treatment options depend on the location and extent of the infection. Mono- or combination therapies involving the use of macrolide, aminoglycoside, and/or other anti-infectious agents may be provided. Debridement and/or surgical removal may be warranted. Treatment durations for disseminated infections can last longer than 6 months. However, uncomplicated, localized infections may resolve on their own with no treatment given (Griffith et al., 2006).

Cutaneous structures are the most common location for M. chelonae infection (Wallace, Brown, & Onyi, 1992), as was the case with this patient. M. chelonae colonization occurs more commonly in immunocompromised and immunosuppressed populations (Redelman-Sidi, & Sepkowitz, 2010). This patient had previously been on immunosuppressive treatments for rheumatoid arthritis (adalimumab, prednisone and leflunomide), many of the drugs used in the treatment of rheumatoid arthritis have broad impact on the immune system in general putting someone taking these medications at greater risk for infection (Schur, 2017).

For this patient the use of tobramycin (intravenous) and clarithromycin (oral) were selected. Tobramycin was chosen based on the results of drug resistance testing performed by a state laboratory. The course of tobramycin treatment was planned for a minimum of four months. A peripherally inserted central catheter (PICC) line was placed in the right upper arm earlier in the day (31 October 2017) in preparation for the tobramycin treatment. The cutaneous lesions on his lower leg were first identified in August 2017 and several other (oral)

antibiotics (linezolid, levofloxin, and sulfamethoxazole) had been tried without success before the decision was made to start tobramycin. Patient denied: fever, chills, shortness of breath, or abdominal pain accompanying the lesions. Patient is a smoker and reported a chronic cough.

This patient has a complex medical history with numerous comorbidities as indicated below with their date of diagnosis: ankle fracture (1978), lumbago (1982), rotator cuff repair (three times, most recently in 2000), total hip replacement (2004), diabetes mellitus type II (2007), neck pain (2008), torn right meniscus (2009), hypertension (2011), hyperlipidemia (2011), carpal tunnel (2011), hearing loss (2011), thigh/pelvic pain (2011), cutaneous infection disease (2017), and candidiasis of the mouth (2017). Current medication besides tobramycin include: duloxetine HCL, clarithromycin, cholecalciferol, pregabalin, Nasonex, and oxycodone.

This patient was known to the Audiology department prior to his baseline testing; he was first evaluated in March 2011 with complaints of hearing loss since the 1970s. At that time, he reported no significant otologic health history (e.g. surgery, TM perforation, recurrent otitis) and denied the presence of or a history of recurrent tinnitus. Otoscopic inspection of the ear canals was unremarkable. Military noise exposure was reported as to jet aircraft without the use of hearing protection devices (HPDs). Occupational noise exposure outside the military was denied. Recreational noise exposure was reported as due to: hunting, power tool use, and motorcycle riding with at least some use of HPDs. Pure tone audiometric testing in 2011 revealed a mild sloping to moderate sensorineural hearing loss 2-8 kHz in the right ear (AD) and moderate to moderately-severe sensorineural hearing loss 3-8 kHz in the left ear (AS). Word recognition (recorded Maryland CNC word list) was excellent at 100% AD and 96% AS. The patient was determined to be a candidate for amplification at that time, but was not interested due to a lack of perceived hearing handicap. A subsequent hearing evaluation in September 2014 revealed a mild sloping to moderately-severe sensorineural hearing loss 2-8 kHz AU with 96% word recognition in each ear (recorded Maryland CNC lists). The patient denied any changes in otologic history other than the change in hearing at this exam. Patient reported an increase in perceived hearing handicap and was issued binaural hearing aids.

The baseline audiometric exam for the aminoglycoside treatment was performed on 31 October 2017 and revealed a mild sloping to moderately-severe sensorineural hearing loss 2-8 kHz AU. Unfortunately, high frequency audiometric testing was not performed. Although the equipment was present in the clinic (high frequency circumaural headphones, Sennheiser HDA200), the

clinic lacked an established protocol for ototoxicity monitoring that included high frequency testing, such as the sensitive range for ototoxicity (SRO) (Konrad-Martin et al., 2014). Only testing at 8 kHz and below carries a substantial risk of missing early damage; establishing a clinical protocol using the SRO method would be of great benefit to patients at this facility. Word recognition performance remained excellent at 96% AD and 100% AS (recorded Maryland CNC lists). Tinnitus was still denied and no changes in hearing or otologic history were reported to have occurred since 2014 exam. The hearing thresholds measured at the baseline exam were consistent with those from the 2014 exam.

Tobramycin treatment was initiated following the patient's Audiology appointment on 31 October 2017, with a loading dose of 180mg via the PICC line and a second dose of 160mg later that evening. The patient remained hospitalized for one week receiving doses of: 160mg every 8 hours the first day, 160mg and 180mg 12 hours apart on day two, and 180mg every 12 hours days 3-6. On the date of discharge (day 7), he was given 180mg prior to discharge followed by a second dose of 260mg later that day at home. Following discharge, he received daily injections (through the PICC line) of 260 mg from a home health service and was seen in the ambulatory treatment unit (ATU) of a satellite VA facility twice a week for his daily dosing to allow for measurement of peak and trough serum levels of tobramycin.

In early December, the patient reported periodic tinnitus during one of his injection appointments in the ATU; tinnitus was reported to have started a few days prior to that appointment (approximately 6 weeks into his treatment). He did not report noticing any change in hearing - only the onset of intermittent tinnitus. The patient was seen within the Audiology department for evaluation 2 days after reporting tinnitus; he again denied noticing any change in his hearing. Audiometric pure tone testing revealed a mild sloping to moderately-severe sensorineural hearing loss 2-8 kHz AD and a mild sloping to moderately-severe sensorineural hearing loss 3-8 kHz AS, no testing beyond 8 kHz was performed at this appointment either. All thresholds at the December exam were +/-5 dB compared to baseline testing (31 October 2017) showing hearing thresholds to be stable (Stuart, Stenstrom, Tompkins, & Vandenhoff, 1991). Patient reported his periodic tinnitus was "annoying but manageable". No balance problems or vertigo were reported to Audiology or the medical team; although, it is not known if he was specifically asked whether he had any of these symptoms.

Treatment was originally scheduled to end on 22 January 2018, but was terminated on 5 January 2018, due to onset of tinnitus during the course of treatment and subsequent finding that the infectious lesions had resolved. At his final appointment within the Infectious Disease department, the patient

reported he experiences tinnitus approximately 2 times per week with the episodes roughly 1 hour in duration. The patient did not feel his hearing had changed over the course of treatment. Per chart notes, Infectious Disease contacted the Audiology department at the satellite facility; the person with whom they spoke (presumably one of the audiologists at that facility) indicated that a post treatment audiological exam was not warranted due to patient denial of any changes. The plan of care suggested for the patient is to self-refer to audiology if he notices any changes in hearing or tinnitus going forward.

Consultation requests

Two urgent (STAT) consultation requests were received by the Audiology department for a patient who was about to be started on long-term tobramycin treatment. The consult for an audiologic baseline exam was filled out completely and it was clear what was being requested. The consult for the vestibular exam was not completed appropriately by the referring provider; only a blank consultation template had been submitted. Since it was unclear what was being requested, an attempt was made to contact this provider prior to the appointment for clarification; this endeavor was unsuccessful. During the appointment, vestibular testing was discussed with the patient. He declined to have any testing as he did not have a history of symptoms related to vestibular dysfunction nor was he currently experiencing any of these symptoms. Given the blank consultation request, the lack of response from the referring provider, and the patient's unwillingness to have testing performed, the vestibular consult was thought to have been entered in error and was cancelled. Subsequently, a comment was entered into the patient's medical record as to why the request was being denied and that if it had not been submitted in error the requester should submit a new appropriately completed consultation request. There was no response to this action.

For clarification purposes, approximately one week later, the referring provider was contacted again. She stated that a vestibular evaluation had been desired and inquired if it should still be pursued if patient was agreeable. As will be discussed in greater detailed below, vestibular testing was not advised given the limited equipment available for testing vestibular function at this facility. Furthermore as discussed earlier in the paper, protocols exist for the monitoring of cochlear function during ototoxic treatment regimens, the same is not true for the monitoring of vestibular function. Given the lack of a recognized monitoring protocol and equipment limitations, the vestibular team determined baseline testing would serve little purpose and testing should only be competed if vestibular symptoms were reported.

Equipment limitations

Currently, the Audiology clinic discussed here has limited space dedicated to the provision of vestibular testing. The available equipment (GN Otometrics Charter 200, NCI-480 water caloric stimulator) can be used to perform the videonystagmography (VNG) test battery, which includes: spontaneous nystagmus tests, positional nystagmus tests, oculomotor testing, and bithermal caloric irrigation. VNG testing is an updated method of measuring nystagmus compared to ENG testing as advocated in Scheenstra et al. (2009). The only difference is that with VNG testing slow phase velocity of nystagmus is measured with infrared video goggles while in ENG slow phase velocity of the nystagmus is measured with surface electrodes.

Caloric responses can vary greatly within patients on repeat testing (Maes, Dhooge, De, D'haenens, Bockstael, & Vinck, 2007) so it would require a large shift in slow phase velocity to say there had actually been a change in function with any degree of confidence. Furthermore, any changes in function would likely be binaural in nature and binaural vestibular hypofunction is not ideally confirmed with caloric testing. Rotary chair testing is the preferred method for long term monitoring of vestibular function due to the consistency of the stimuli (Jacobson & Shepard, 2008). The opinions of two outside colleagues and experienced experts in vestibular evaluation were sought for this case. Both agreed that VNG was not the ideal way to monitor vestibular function as there is not much evidence regarding sensitivity of the measure for tracking vestibulopathy. The caloric test is a somewhat noxious test for an otherwise healthy patient - let alone one who is medically fragile or ill. Caloric testing measures very low frequency movement and might not show changes even if there was damage to the system. Monitoring for the development of spontaneous nystagmus and using rotational testing were suggested as preferable ways to monitor for any changes in vestibular function.

Lessons Learned

Patient care when using ototoxic drugs (e.g. tobramycin) is optimized by mitigating potentially avoidable cochleotoxicity or vestibulotoxicity through clear communication between care team members. Cochleotoxicity is often at the forefront of concerns relating to the provision of ototoxic pharmaceutical agents, however, vestibulotoxicity should also be considered as loss of vestibular function can have a severe impact on quality of life. Medical providers also need to be familiar with this aspect as indicated in Halmagyi et al., (1994). The

greatest lesson learned here is that clear communication channels, education of audiology staff, and education of medical staff are needed.

In this instance, a communication breakdown occurred following an entry of an incomplete consultation request. The referring provider did not respond to the initial inquiry for clarification, which lead to the (incorrect) presumption that the request had been entered in error and was subsequently cancelled. Following standard clinical practices for the facility resulted in the generation of a view alert in the medical record system, which the referring provider could see the next time she logged into the system. Direct communication with the provider through email resulted in a more timely response that enabled relevant discussions.

An educational opportunity was provided through this case for audiologists to learn more about aminoglycoside antibiotics, their potential for vestibulotoxic effects, and the need to monitor for damage to the vestibular system. Black et al (2001) recommended monitoring vestibular function prior to, throughout and following ototoxic drug administration as symptoms of bilateral hypofunction is not always readily apparent. Audiological care for Veterans is all too often thought of as simply providing hearing aids as management for the combination of presbycusis and noise-induced hearing loss. This case demonstrates the wider range of opportunities for audiological care.

An additional educational opportunity provided through this case is that the medical staff would benefit from education regarding what services the Audiology department currently can and cannot offer in regard to ototoxic monitoring. Plans are in the works to provide this education during a future staff meeting of medical providers at the facility.

The most tangible outcome here may be that this case provides additional justification for the established and repeated requests to obtain further vestibular test equipment (rotary chair, vestibular evoked myogenic potential (VEMP) system, and video head impulse test (vHIT) equipment), as an additional unmet need has been identified. The loss of hair cells along with other types of cells in the utricle and saccule (Pauna et al., 2017) support the procurement of equipment capable of performing vestibular evoked myogenic potentials (VEMPs) enabling the measurement of otolith function in addition to semi-circular canal function. Given that the rotary chair only measures function of the horizontal canal he addition of vHIT allows for measurement of superior and posterior canal function which were also shown to be impacted in Pauna et al., (2017).

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TOWARDS A FUTURE WITHOUT OTOTOXICITY

Our ability to hear and maintain postural control can be affected by many factors, including congenital genetic mutations, aging, noise exposure, trauma, selected infections, and a variety of environmental exposures and pharmaceutical interventions. Ototoxicity refers to the damage of the inner ear, specifically cochlear and vestibular structures and functions, as the result of exposure to pharmaceuticals, chemicals, and/or ionizing radiation. Ototoxic compounds can also damage the auditory and/or vestibular neural pathways to the brain's cortex; however, we generally define ototoxicity as affecting the peripheral inner ear, inducing auditory dysfunction (cochleotoxicity) or vestibular deficits (vestibulotoxicity).

Aminoglycoside antibiotics, cisplatin and other platinum-based drugs, loop diuretics, and cyclodextrins, a newly-identified ototoxin, are all discussed in a special Research Topic edition of Frontiers in Cellular Neuroscience, entitled *Cellular Mechanisms in Ototoxicity*. Articles include both original research articles and also focused reviews on topics in areas undergoing rapid growth in empirical data that need to be integrated into an over-arching theme of further hypothesis-driven research for validation. Although aminoglycoside antibiotics (Jiang et al., 2017a) and platinum-based drugs (Sheth et al., 2017) are the primary ototoxins reviewed in this special issue, articles also focused on characterizing their mechanisms of cytotoxicity and cell death (Francis and Cunningham, 2017; Nicholas et al., 2017). Several articles extend this criterion to discuss how candidate otoprotectants revealed and/or ameliorated mechanisms of ototoxicity (Fransson et al., 2017; Jadali et al., 2017; Kirkwood et al., 2017; Ramaswamy et al., 2017; Wiedenhoft et al., 2017).

Importantly, these studies build the existing knowledge base to direct future research towards (i) understanding the mechanisms of how individual ototoxins - including a recently identified ototoxin (Crumling et al., 2017) - cause drug-induced cochleotoxicity and vestibulotoxicity (Sultemeier and Hoffman, 2017), and (ii) efficacious identification of pharmaceutical interventions to prevent ototoxicity (Noack et al., 2017; O'Sullivan et al., 2017; Kim et al., 2018). These include co-therapeutics, as well as identifying non-ototoxic drugs or revised dosing paradigms that are non-ototoxic. In addition, candidate otoprotective strategies can inadvertently potentiate ototoxicity, especially when tested in mammalian explants, following initial characterization in zebrafish lateral line studies (Majumder et al., 2017; Yang et al., 2017). The future for determining the efficacy of lead candidate otoprotectants against

ototoxicity, and noise-induced hearing loss will be accelerated by the translation of candidate compounds into human clinical trials, an emerging area of discussion during PIHL teleconference calls for both the Ototoxicity and the Drugs Committees.

With the recent identification of inflammation as a factor that synergistically potentiates ototoxicity, three articles explored how inflammation plays a crucial role during ototoxicity and the healing process (Jiang et al., 2017b; Kalinec et al., 2017; Mwangi et al., 2017; Wood and Zuo, 2017). This arena will continue to grow, as will another area of crucial importance, antibiotic stewardship to preserve the anti-bacterial efficacy of antibiotics as bacteria continue to develop resistance to the current armamentarium of antibiotics. Similar concerns are also prevalent in cisplatin-induced ototoxicity where the candidate otoprotectant may also inadvertently protect tumor cells from the cytotoxic effects of anti-neoplastic agents. Another under-explored area of increasing interest is the role of microRNAs in disease and infections, including ototoxicity and noise-induced hearing loss (Prasad and Bondy, 2017).

These articles are open access (i.e., freely accessible on the internet) and contribute to the increasing societal awareness of hearing loss, especially acquired hearing loss from noise, drugs or aging. Currently, sensorineural hearing loss is irreversible, and protecting sensorineural hearing can be readily achieved, both now and in the near future, compared to the longer-term development of a viable clinical intervention to restore hearing. Protection, repair, rehabilitation and ultimately restoration, of our ability to hear and remain cognitively able to sustain our familial, friendship and professional connections will enhance our quality of life individually and throughout society.

On behalf of all the authors in this Research Topic, I want to thank the Department of Defense Hearing Center of Excellence for their support in ensuring these articles are freely accessible to all, and for providing personnel time and resources to coordinate contributing scientists to discuss ototoxicity via teleconference calls. Without this support, these contributions to the scientific literature would not have been possible, and we as scientists benefit by conducting more focused - and readily accessible - research as we move forwards towards a future free of ototoxicity.

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RECENTLY PUBLISHED LITERATURE

Articles determined to be of particular interest will be listed with full abstract in "Research Highlights" below, followed by the remainder of the "Relevant Literature," all published between October 2016 (the end of the last Newsletter search term) and December 2017.

RESEARCH HIGHLIGHTS

Editors evaluated over 296 article abstracts and full text articles as needed for inclusion in this edition's listing of recently published PIHL-related literature. While the final retention of articles was a subjective decision by the editors, care was taken to ensure that articles met at least a basic criterion of relevance or interest to the PIHL community, with a focus on interests of the Ototoxicity Committee and subcommittee. Articles which examined ototoxic drugs in isolation were generally not retained while those examining drugs to prevent or mitigate ototoxicity were included, for example. Likewise, studies about efficacy of hearing conservation programs or industrial hygiene were not included, nor properly searched for, but select studies with relevance to PIHL-related population selection or study design implications have been included. Searching only PubMed, the following search was conducted:
"Ototoxicity": 296 articles reviewed by abstract, 265 retained; 38 selected, 9 abstracts highlighted below.

The Incidence of Ototoxicity in Patients Using Iron Chelators.
Derin S, Azık FM, Topal Y, Topal H, Karakuş V, Çetinkaya PU, Şahan M, Azık TE, Kocabaş CN. J Int Adv Otol. 2017 Apr;13(1):136-139. doi: 10.5152/iao.2016.1852. Epub 2016 Nov 23.

Abstract

Objective: In this study, we aimed to detect the incidences of ototoxicity in patients with hemoglobinopathies taking deferoxamine (DFO), deferiprone, and deferasirox using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) scale to obtain more objective data.

Materials and Methods: Fifty-five transfusion-dependent patients were evaluated in this study. The NCI CTCAE scale was used to assess ototoxicity levels. The average ferritin and hemoglobin levels, the type of iron chelator, and the duration of therapy of all the patients were recorded.
Results: Ototoxicity was observed in 15 patients (31.9 %), all of whom were taking DFO. The median age was 19.5 (6-43) in patients without ototoxicity and 29 (16-50) in those with ototoxicity; this difference was statistically significant ($p<0.05$). The median ferritin and pre-tx Hb levels were 1391 ng/mL and 9.06 mg/dL, respectively, in patients with ototoxicity and 986.7 ng/mL and 9.24 mg/dL, respectively, in those without ototoxicity; these differences were not significant ($p>0.05$). Ototoxicity was not observed in the eight patients who used only deferasirox and deferiprone.
Conclusion: The ototoxicity incidence with DFO at doses below 50 mg/kg/day was 27.3%. Deferiprone and deferasirox were not associated with ototoxic effects in patients taking these drugs.

Prevalence of hearing and vestibular loss in cystic fibrosis patients exposed to aminoglycosides.

Handelsman JA, Nasr SZ, Pitts C, King WM. Pediatr Pulmonol. 2017 Sep;52(9):1157-1162. doi: 10.1002/ppul.23763. Epub 2017 Jul 24.

Abstract

Aim: Cystic Fibrosis (CF) patients frequently use aminoglycosides (AGS) to treat CF exacerbation due to colonization with Pseudomonas aeruginosa. Although AGS can cause vestibular and auditory sensory losses that can negatively impact quality of life, little is known about the prevalence of vestibular loss in this population. The aim of this study was to determine the prevalence of hearing loss and/or vestibular dysfunction in CF patients treated with AGS.
Methods: The relationship between hearing status and vestibular status was also investigated. Hearing was determined to be normal or abnormal based on pure tone air and bone conduction thresholds. Vestibular outcome was divided into four categories; normal, non-lateralized vestibular dysfunction, unilateral loss, and bilateral loss based on results of post head shaking testing, positional and positioning testing, bithermal calorics, sinusoidal, and rotational step testing.
Results: Of our cohort of 71 patients, 56 (79%) patients have vestibular system dysfunction while only 15 (21%) have normal vestibular system function. Overall, 16 patients (23%) have hearing loss. In considering the relationship between auditory and vestibular function, 12 (17%) demonstrated both normal hearing and normal vestibular function and 13 (18%) have both hearing loss and abnormal vestibular function. Of the 55 (78%) patients with normal hearing, 43

(61%) have vestibular dysfunction, while 3 (4%) of patients with normal vestibular function have hearing loss.
Conclusion: These results suggest that monitoring hearing alone is insufficient to detect ototoxicity in CF patients being treated with systemic AGS.

Risk of sensorineural hearing loss with macrolide antibiotics: A nested case-control study

Etminan M, Westerberg BD, Kozak FK, Guo MY, Carleton BC. Laryngoscope. 2017 Jan;127(1):229-232. doi: 10.1002/lary.26190. Epub 2016 Aug 6.

Abstract

Objective: To determine the association between a diagnosis of sensorineural hearing loss (SNHL) and the prescription of a macrolide antibiotic.
Study Design: Retrospective nested case-control study.
Methods: From the LifeLink (IMS, Danbury, CT) health claims database, we randomly selected a cohort of subjects 15 to 60 years old from 2006 to 2014. Cases were identified as patients diagnosed with SNHL, each matched by age and calendar time to 10 controls selected from the same cohort. All macrolide prescriptions (erythromycin, azithromycin, clarithromycin, and telithromycin) were identified, and statistical comparison of usage was compared between cases and controls. Amoxicillin and fluoroquinolone antibiotics were used as positive controls to further investigate confounding by infection. Albuterol was used as a negative control because this is a drug class not expected to be associated with SNHL or with a confounding condition potentially causing SNHL.
Results: From a cohort of 6,110,723 subjects, we identified 5,989 cases of SNHL and 59,890 corresponding controls. The rate ratio for one prescription of a macrolide was 1.36 (95% confidence inteval [CI]: 1.24-1.49) and for multiple prescriptions was 1.66 (95% CI: 1.42-1.94). Similar rate ratios were observed with multiple prescriptions of amoxicillin and fluoroquinolones.
Conclusion: A significant association between SNHL and macrolide use was likely due to confounding by indication for antibiotic treatment because the risk was also observed with fluoroquinolones and amoxicillin, antibiotics with no known ototoxicpotential. Therefore, there does not appear to be an increased risk of SNHL in patients treated with macrolide antibiotics.
LEVEL OF EVIDENCE: 3b. Laryngoscope, 127:229-232, 2017.

Macrolide-associated sensorineural hearing loss: A systematic review

Ikeda AK, Prince AA, Chen JX, Lieu JEC, Shin JJ. Laryngoscope. 2017 Aug 3. doi: 10.1002/lary.26799. [Epub ahead of print]

Abstract

Objectives: To investigate the potential association of macrolide antibiotics with sensorineural hearing loss (SNHL) and which agents and dosage may be related. To evaluate whether an optimal treatment exists for reversing SNHL that occurs after macrolide therapy.

Study Design: Systematic review of the literature.

Methods: Computerized (PubMed, EMBASE, Cochrane Library) and manual searches were performed to identify human studies of all ages (patients) who received macrolides (intervention, with or without control) and documented SNHL (outcome). All study designs were assessed. Extracted data included macrolide regimen details, as well as the timing, severity, and reversibility of SNHL with drug cessation alone or with additional medical intervention. Study designs and the associated risk of bias were assessed.

Results: The 44 publications (3 prospective, 41 retrospective) that met these criteria described 78 cases of audiometrically confirmed SNHL. SNHL was associated with oral and intravenous macrolide administration at standard and elevated doses. SNHL was irreversible in six cases, despite macrolide cessation (n = 5) and oral steroid treatment (n = 1). Irreversible SNHL was observed following 2 to 3 days of exposure. SNHL was reversible with macrolide cessation alone in 70 cases. In two cases, macrolide cessation coupled with oral steroid administration restored hearing. Reversible cases improved within hours to days. Nine studies also described 42 cases of subjective patient-reported hearing loss. Limitations in the data arose from study design, related comorbidities, and concomitant drug administration.

Conclusion: SNHL may follow macrolide exposure, even at standard oral doses. Further research is needed to understand the incidence, prevalence, and biological mechanism of its ototoxicity. Laryngoscope, 2017.

Evaluation of the Ototoxicity Potential of Once-Daily, Single-Entity Hydrocodone in Patients with Chronic Pain: Results of Two Phase-3 Clinical Studies

Campbell K, Kutz JW Jr, Shoup A, Wen W, Lynch SY, He E, Ripa SR. Pain Physician. 2017 Jan-Feb;20(1):E183-E193.

Abstract

Background: Use/misuse of the opioid combination hydrocodone-acetaminophen has been associated with permanent hearing loss. Although reports have been rare, this potential effect can have significant detrimental effect on patients' overall quality of life. To date, the ototoxic effect of hydrocodone alone has not been systematically investigated.

Objective: In this report, we aimed to evaluate the potential ototoxicity of a novel, single-entity, once-daily, extended-release hydrocodone tablet (Hysingla® ER; HYD).
Methods: Results from 1207 patients in two phase 3 clinical studies were evaluated: A placebo-controlled study with an enriched enrollment, randomized withdrawal design in patients with chronic low back pain, and an open-label, long-term, safety study in patients with chronic nonmalignant and non-neuropathic pain. Comprehensive audiologic assessments (comprising pure-tone air-conduction audiometry in the conventional [0.25-8 kHz] and ultra-high [10-16 kHz] frequencies, pure-tone bone-conduction audiometry, tympanometry, speech reception thresholds, and word recognition) were conducted at baseline and end-of-studies; air-conduction audiometry was conducted periodically during the studies. All audiologic assessments were performed in audiology clinics in the United States by licensed audiologists. The primary endpoint was changes from baseline in pure-tone air-conduction thresholds in the conventional frequencies during the studies. These trials are registered with ClinicalTrials.gov, identifiers NCT01400139 and NCT01452529.
Results: During the studies, mean changes from baseline in air-conduction thresholds were clinically unremarkable. Bidirectional variability across all test frequencies was observed; 82% of patients did not experience significant threshold changes during the studies, 7% had potential hearing decrement, and 10% experienced hearing sensitivity improvement. No notable differences were observed between patients receiving HYD and placebo or between different HYD doses.
Conclusion: No ototoxic signal was observed for single-entity hydrocodone tablets at the dosages and treatment durations investigated. Key words: Audiologic monitoring, clinical trials, hydrocodone, opioids, ototoxicity monitoring, sensorineural hearing loss.

Cisplatin is retained in the cochlea indefinitely following chemotherapy

Breglio AM, Rusheen AE, Shide ED, Fernandez KA, Spielbauer KK, McLachlin KM, Hall MD, Amable L, Cunningham LL. Nat Commun. 2017 Nov 21;8(1):1654. doi: 10.1038/s41467-017-01837-1.

Abstract

Cisplatin chemotherapy causes permanent hearing loss in 40-80% of treated patients. It is unclear whether the cochlea has unique sensitivity to cisplatin or is exposed to higher levels of the drug. Here we use inductively coupled plasma mass spectrometry (ICP-MS) to examine cisplatin pharmacokinetics in the cochleae of mice and humans. In most organs cisplatin is detected within one

hour after injection, and is eliminated over the following days to weeks. In contrast, the cochlea retains cisplatin for months to years after treatment in both mice and humans. Using laser ablation coupled to ICP-MS, we map cisplatin distribution within the human cochlea. Cisplatin accumulation is consistently high in the stria vascularis, the region of the cochlea that maintains the ionic composition of endolymph. Our results demonstrate long-term retention of cisplatin in the human cochlea, and they point to the stria vascularis as an important therapeutic target for preventing cisplatin ototoxicity.

Autophagic flux, a possible mechanism for delayed gentamicin-induced ototoxicity

Kim YJ, Tian C, Kim J, Shin B, Choo OS, Kim YS, Choung YH.
Sci Rep. 2017 Feb 1;7:41356. doi: 10.1038/srep41356.

Abstract

Aminoglycoside antibiotics including gentamicin (GM) induce delayed ototoxic effects such as hearing loss after long-term use, unlike the early-onset ototoxicity caused by cisplatin. The purpose of the study was to identify the mechanism of the delayed GM-induced ototoxicity by exploring the role of autophagy in vitro and in vivo. Treating HEI-OC1 auditory cells with GM led to a time-dependent increase of the autophagosome marker LC3-II, which was accompanied by cell death. In contrast, cisplatin and penicillin caused a rapid increase and had no effect on LC3-II levels, respectively. LC3-II-expressing autophagosomes co-localized with the labeled GM. GM-treated autophagosomes expressed reduced levels of Rab7, which is necessary for the fusion of autophagosomes with lysosomes. When the autophagic flux enhancer rapamycin was applied to GM-treated cells, Rab7 and the lysosomal enzyme cathepsin D were upregulated, and increased cell survival was observed. In animal studies, the intraperitoneal injection of GM worsened hearing thresholds and induced the accumulation of LC3 in the organ of Corti. This hearing impairment was attenuated by rapamycin. These findings suggest that the delayed onset-ototoxicity of GM may be closely related to the accumulation of autophagosomes via impaired autophagy. This GM-induced auditory cell death could be inhibited by enhancing autophagic flux.

Pre-conditioning with near infrared photobiomodulation reduces inflammatory cytokines and markers of oxidative stress in cochlear hair cells

Bartos A[1], Grondin Y[1], Bortoni ME[1], Ghelfi E[1], Sepulveda R[1], Carroll J[2], Rogers RA[1].
J Biophotonics. 2016 Dec;9(11-12):1125-1135. doi: 10.1002/jbio.201500209. Epub 2016 Jan 21.

Abstract

Hearing loss is a serious occupational health problem worldwide. Noise, aminoglycoside antibiotics and chemotherapeutic drugs induce hearing loss through changes in metabolic functions resulting in sensory cell death in the cochlea. Metabolic sequelae from noise exposure increase production of nitric oxide (NO) and Reactive Oxygen Species (ROS) contributing to higher levels of oxidative stress beyond the physiologic threshold levels of intracellular repair. Photobiomodulation (PBM) therapy is a light treatment involving endogenous chromophores commonly used to reduce inflammation and promote tissue repair. Near infrared light (NIR) from Light Emitting Diodes (LED) at 810 nm wavelength were used as a biochemical modulator of cytokine response in cultured HEI-OC1 auditory cells placed under oxidative stress. Results reported here show that NIR PBM at 810 nm, 30 mW/cm^2 , 100 seconds, 1.0 J, 3 J/cm^2 altered mitochondrial metabolism and oxidative stress response for up to 24 hours post treatment. We report a decrease of inflammatory cytokines and stress levels resulting from NIR applied to HEI-OC1 auditory cells before treatment with gentamicin or lipopolysaccharide. These results show that cells pretreated with NIR exhibit reduction of proinflammatory markers that correlate with inhibition of mitochondrial superoxide, ROS and NO in response to continuous oxidative stress challenges. Non-invasive biomolecular down regulation of proinflammatory intracellular metabolic pathways and suppression of oxidative stress via NIR may have the potential to develop novel therapeutic approaches to address noise exposure and ototoxic compounds associated with hearing loss.

Styrene enhances the noise induced oxidative stress in the cochlea and affects differently mechanosensory and supporting cells

Fetoni AR[1], Rolesi R[2], Paciello F[3], Eramo SLM[4], Grassi C[4], Troiani D[4], Paludetti G[2].

Free Radic Biol Med. 2016 Dec;101:211-225. doi: 10.1016/j.freeradbiomed.2016.10.014. Epub 2016 Oct 18.

Abstract

Experimental and human investigations have raised the level of concern about the potential ototoxicityof organic solvents and their interaction with noise. The main objective of this study was to characterize the effects of the combined noise and styrene exposure on hearing focusing on the mechanism of damage on the sensorineural cells and supporting cells of the organ of Corti and neurons of the ganglion of Corti. The impact of single and combined exposures on hearing was evaluated by auditory functional testing and histological analyses of cochlear specimens. The mechanism of damage was studied by analyzing superoxide anion and lipid peroxidation expression and by computational

analyses of immunofluorescence data to evaluate and compare the oxidative stress pattern in outer hair cells versus the supporting epithelial cells of the organ of Corti. The oxidative stress hypothesis was further analyzed by evaluating the protective effect of a Coenzyme Q_{10} analogue, the water soluble Q_{ter}, molecule known to have protective antioxidant properties against noise induced hearing loss and by the analysis of the expression of the endogenous defense enzymes. This study provides evidence of a reciprocal noise-styrene synergism based on a redox imbalance mechanism affecting, although with a different intensity of damage, the outer hair cell (OHC) sensory epithelium. Moreover, these two damaging agents address preferentially different cochlear targets: noise mainly the sensory epithelium, styrene the supporting epithelial cells. Namely, the increase pattern of lipid peroxidation in the organ of Corti matched the cell damage distribution, involving predominantly OHC layer in noise exposed cochleae and both OHC and Deiters' cell layers in the styrene or combined exposed cochleae. The antioxidant treatment reduced the lipid peroxidation increase, potentiated the endogenous antioxidant defense system at OHC level in both exposures but it failed to ameliorate the oxidative imbalance and cell death of Deiters' cells in the styrene and combined exposures. Current antioxidant therapeutic approaches to preventing sensory loss focus on hair cells alone. It remains to be seen whether targeting supporting cells, in addition to hair cells, might be an effective approach to protecting exposed subjects.

RELEVANT LITERATURE

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CLINICAL TRIALS

ClinicalTrials.gov was searched using the following search terms: “ototoxicity”, “noise induced hearing loss,” “hearing loss” AND “pharmaceutical” and “tinnitus” AND “pharmaceutical.” “Include only open studies” was selected and the search results, retrieved December 2017, derived 10, 2, 32 and 8 results, respectively, for a total of 52 results. 16 duplicates were removed leaving 36 studies for review. Studies were further eliminated from inclusion based on subjective determination of relevance by the editors for a total of 24 studies included below. It should be noted that relevance was considered broadly as any studies of potential interest, including in secondary outcomes listed, to any one of the PIHL committee focus areas (see editor’s introduction for the general listing of these). An exception to the PIHL focus areas used was the category of noise exposure, to include both measurement and preventative assessments, as this opens such a large category of studies, not all of which would necessarily categorize as a clinical trial nor be required to register in clinicaltrials.gov, and thus inclusion herein would produce an indeterminately incomplete set. In studies where primary or secondary outcomes assessed an intervention for hearing or tinnitus outcomes the studies were included, whereas studies which only captured hearing or tinnitus outcomes as adverse events were excluded. This most predominantly occurred in ototoxicity studies. All studies are listed in chronological order (using study start date), newest first.

TITLE: A Phase 2b, Randomized, Double-blinded, Placebo-controlled Study to Evaluate the Safety and Efficacy of SPI-1005 to Reduce the Incidence, Severity and Duration of Acute Noise Induced Hearing Loss (NIHL)
CT.gov ID: NCT02779192
Responsible Party: Sound Pharmaceuticals, Incorporated
Target Condition(s): Noise Induced Hearing Loss
Intervention: Drug: SPI-1005 200mgDrug: SPI-1005 400mgDrug: Placebo
Phase: 2
Study Start Date: Feb-18

Description Provided: PI-1005 is a novel oral drug that contains a glutathione peroxidase mimetic (ebselen) that will be tested in subjects with a history of NIHL at risk for additional NIHL. The goal of this multi-center Phase 2b study is to determine whether SPI-1005 is effective in reducing an acute NIHL in this affected population. In this Phase 2b study subjects with prior NIHL will be enrolled and exposed to a calibrated sound challenge (CSC) that induces a slight acute NIHL.
URL:
https://clinicaltrials.gov/ct2/show/NCT02779192?term=NCT02779192&rank=1

TITLE: A Phase III Multicenter, Double-blind, Placebo-controlled, Study Evaluating the Safety, and Efficacy of STR001 Treatment in Adults With Sudden Sensorineural Hearing Loss
CT.gov ID: NCT03331627
Responsible Party: Strekin AG
Target Condition(s): Acute hearing loss
Intervention: Drug: STR001-IT and STR001-ER
Phase: 3
Study Start Date: Feb-18
Description Provided: a multicenter, double-blind, placebo-controlled study in patients with Sudden Sensorineural Hearing Loss (SSHL). Patients will be treated with STR001 thermogel (STR001-IT) / STR001 tablets (STR001-ER) and corresponding Placebo on top of standard of care.
URL:
https://clinicaltrials.gov/ct2/show/NCT03331627?term=NCT03331627&rank=1

TITLE: Observational Study of Hearing Loss and the Effects of Statin Drugs in Head and Neck Squamous Cell Carcinoma Patients Treated With Cisplatin Chemoradiation
CT.gov ID: NCT03225157
Responsible Party: National Institute on Deafness and Other Communication Disorders (NIDCD)
Target Condition(s): Head and Neck Cancer, Hearing Disorder, Hyperlipidemia
Intervention: Not Provided
Phase:
Study Start Date: Dec-17
Description Provided:
Background: Cisplatin is a chemotherapy drug. It is used to treat head and neck squamous cell carcinoma (HNSCC) and other cancers. It can cause hearing loss for

some people. It is not known how many people will get hearing loss from cisplatin. It is also not known what other factors might influence who gets hearing loss. Factors could include age, sex, noise exposure, and other drugs the person is taking. Statins are drugs used to lower cholesterol. Statins may also reduce cisplatin-induced hearing loss.
Objectives: To see if statins reduce hearing loss in people getting cisplatin therapy to treat HNSCC. To find out how many people taking cisplatin get hearing loss from it. To find out if other factors might influence whether cisplatin causes hearing loss.
Eligibility: People ages 18 and older who are getting treatment with cisplatin for HNSCC
Design: Participants will be screened with a review of their medical records. Participants will have 3 visits. These will be before the onset of cisplatin therapy, at about 4 weeks after they finish therapy, and about 6 months after they finish therapy. Each visit will include: Medication history, Audiogram/hearing tests. Participants will wear headphones and indicate when they hear different sounds. Questions about their noise exposure history and whether they have ringing in the ears.
URL:
https://clinicaltrials.gov/ct2/show/NCT03225157?term=NCT03225157&rank=1

TITLE: Investigation of the NMDA Antagonist Ketamine as a Treatment for Tinnitus
CT.gov ID: NCT03336398
Responsible Party: New York State Psychiatric Institute
Target Condition(s): Tinnitus
Intervention: Drug: Ketamine Hydrochloride in saline, Drug: Saline
Phase: 2
Study Start Date: Dec-17
Description Provided: Tinnitus has a prevalence of approximately 1 in 10 adults in the United States. Among those with tinnitus, 36% had nearly constant symptoms and almost 30% of those report that their tinnitus as a big or a very big problem. Currently there are few effective treatments for tinnitus, and no approved medications. Cognitive behavioral and retraining therapy provide some relief, but many patients fail to respond.

Animal research and human studies indicate that maladaptive plasticity plays a role in tinnitus, which involves glutamatergic signaling largely at the NMDA and AMPA receptors. Additionally, GABA signaling has been shown to be impaired in tinnitus. Rodent models show a diminished sensitivity to GABA signaling and human magnetic resonance spectroscopy (MRS) studies show decreased GABA levels in the auditory cortex.

Ketamine is a non-competitive NMDA receptor antagonist that has also been shown to activate AMPA receptors, and modulates ongoing plasticity. Additionally, ketamine activates a subpopulation of cortical GABAergic interneurons and projection neurons and increases GABA levels in the human brain, measured with MRS. Ketamine is FDA approved as an anesthetic, and recent work has demonstrated its efficacy in treating refractory depression and chronic pain. Importantly, these demonstrate that low dose ketamine, at doses lower than those required for anesthesia, are effective in lifting depressed mood and improving the sensation of chronic pain.

For many, tinnitus has an important affective component to it, with distress and co-morbid symptoms of depression and anxiety. The onset and severity of tinnitus can correlate with stressful events, and it has been posited that stress lowers the threshold of perception, and unmasks tinnitus. Tinnitus then triggers more anxiety and depressed mood, which in turn reinforces the symptoms. An advantage of ketamine may be its effect on depression and anxiety, in addition to tinnitus, to interrupt this cycle.

The goal of this study is to perform a proof-of-concept preliminary study of ketamine in tinnitus associated with sensori-neural hearing loss. This will be studied both in participants who report depressed mood and anxiety and those who do not. MRS imaging will be used to assess ketamine-induced changes in GABA in the auditory cortex.

URL:
https://clinicaltrials.gov/ct2/show/NCT03336398?term=NCT03336398&rank=1

TITLE: Triamcinolone Levels in Cochlear Perilymph
CT.gov ID: NCT03248856
Responsible Party: Christoph Arnoldner
Target Condition(s): Cochlear Hearing Loss
Intervention: Drug: Triamcinolone Acetonide
Phase: 1
Study Start Date: Oct-17
Description Provided: In this study Triamcinolone acetonide will be applied intratympanically before cochlear implant surgery. After round window exposure, a perilymph sample and simultaneously a blood sample will be drawn. Triamcinolone levels will then be analyzed in the samples.
URL:
https://clinicaltrials.gov/ct2/show/NCT03248856?term=NCT03248856&rank=1

TITLE: A Phase 2b, Randomized, Double-Blind, Placebo-Controlled Study To Evaluate The Safety And Efficacy of SPI-1005 in Meniere's Disease
CT.gov ID: NCT03325790
Responsible Party: Sound Pharmaceuticals, Incorporated
Target Condition(s): Meniere's Disease
Intervention: Drug: 200mg SPI-1005 BIDDrug: 400mg SPI-1005 BIDOther: Placebo
Phase: 2
Study Start Date: Sep-17
Description Provided: Study participants will be randomized to SPI-1005 or placebo in this double-blind study to evaluate both safety and efficacy of the investigational treatment. Participants, aged 18-75 years, with probable or definite Meniere's disease will undergo baseline testing to assess severity of sensorineural hearing loss, tinnitus and vertigo. During the study, and 28 days after completion of treatment, participants will be evaluated for safety (adverse events, physical examinations, vital signs and clinical laboratory testing (CBC,serum chemistry). Trough plasma levels of ebselen and its major metabolite will be determined using liquid chromatography-mass spectrometry (LCMS) at specified visits. Additionally, plasma will be analyzed for selenium at the corresponding visits. The effect of SPI-1005 on hearing and balance will be evaluated. Tinnitus (TFI) and vertigo (VSS) will be evaluated at baseline, during and study treatment.
URL:
https://clinicaltrials.gov/ct2/show/NCT03325790?term=NCT03325790&rank=1

TITLE: High Dose Oral Steroids in Sudden Sensorineural Hearing Loss
CT.gov ID: NCT03255473
Responsible Party: University of Colorado, Denver
Target Condition(s): Sudden Sensorineural Hearing Loss (SSNHL)
Intervention: Drug: DexamethasoneDrug: Prednisone
Phase: 2
Study Start Date: Aug-17
Description Provided: Sudden sensorineural hearing loss (SSNHL) affects approximately 5 to 20 per 100,000 persons with spontaneous recovery seen in 32% to 65%. Many different treatments have been investigated in attempt to improve hearing outcomes, with oral corticosteroids having some success. Steroid regimens are highly variable, however, retrospective data has suggested greater improvement in hearing outcomes with the use of high dose oral steroids (dexamethasone) in the setting of unilateral sudden sensorineural hearing loss compared to traditional medical therapy with lower dose oral prednisone. The

investigators hypothesize that patients with unilateral SSNHL who are randomized to treatment with high doses of oral dexamethasone will show better hearing outcomes than patients who are randomized to the more common standard clinical practice treatment with lower doses of oral prednisone.
URL:
https://clinicaltrials.gov/ct2/show/NCT03255473?term=NCT03255473&rank=1

TITLE: First in Human Safety Study of FX-322 in Adults Undergoing Cochlear Implantation
CT.gov ID: NCT03300687
Responsible Party: Frequency Therapeutics
Target Condition(s): Hearing Loss
Intervention: Drug: FX-322, Drug: Placebo
Phase: 1
Study Start Date: May-17
Description Provided: Approximately 12 participants will be enrolled in the study. Assessed will be safety and tolerability of FX-322 administered by intratympanic injection. Also assessed will be the FX-322 concentration in cochlear fluid (perilymph), the pharmacokinetic (PK) profile of FX-322 to determine the systemic exposure to FX-322.
URL:
https://clinicaltrials.gov/ct2/show/NCT03300687?term=NCT03300687&rank=1

TITLE: Combination of Hearing Rehabilitative Interventions and Huperzine A for Presbycusis Related Tinnitus Suppression, Hearing and Cognitive Function Protection in Presbycusis
CT.gov ID: NCT03101722
Responsible Party: Zhijun Bao
Target Condition(s): Presbycusis, Tinnitus, Cognitive Impairment
Intervention: Device: digital hearing aids, Drug: Huperzine A, Other: digital hearing aids and Huperzine A, Other: placebo
Phase: Not Provided
Study Start Date: May-17
Description Provided: To investigate the effects of hearing aid, huperzine A and combination of hearing aid and huperzine A on tinnitus suppression, hearing and cognitive function protection in patients with presbycusis.
URL:
https://clinicaltrials.gov/ct2/show/NCT03101722?term=NCT03101722&rank=1

TITLE: A Pilot Trial of Rilonacept for Treatment of Autoimmune Neurosensory Hearing Loss
CT.gov ID: NCT02828033
Responsible Party: Stanley Cohen
Target Condition(s): Autoimmune Neurosensory Hearing Loss (ANSHL)
Intervention: Drug: Rilonacept
Phase: 1
Study Start Date: Feb-17
Description Provided: Ten (10) patients in total will be enrolled in this study at Metroplex Clinical Research Center in Dallas, TX. Patients may be identified and referred by local area audiologist. The ANSHL study population will be defined by inclusion and exclusion criteria designed to limit enrollment to individuals with idiopathic, progressive, bilateral sensorineural hearing loss, to ensure appropriate candidates for treatment with study medications, and to identify those with a high likelihood of complying with the study protocol.

TITLE: Efficacy and Safety of AM-111 as Acute Sudden Sensorineural Hearing Loss Treatment
CT.gov ID: NCT02809118
Responsible Party: Auris Medical, Inc.
Target Condition(s): Hearing Loss, Idiopathic Sudden Sensorineural
Intervention: Drug: AM-111 0.4 mg/mlDrug: AM-111 0.8 mg/mlOther: Placebo
Phase: 3
Study Start Date: Jun-16
Description Provided: This is a Phase III, randomized, double-blind, placebo-controlled, parallel group, multi-center, efficacy and safety trial of AM-111 in the treatment of subjects suffering from severe to profound idiopathic sudden sensorineural hearing loss.
The active pharmaceutical ingredient of AM-111 is a JNK inhibitor (D-JNKI-1), a synthetic peptide consisting of 31 D-amino acids, which acts as a c-Jun N-terminal kinase (JNK) ligand.
The study consists of one treatment visit and a follow-up period until day 91. Study participants will receive, after topical anesthesia of the tympanic membrane, AM-111 0.4 mg/mL or 0.8 mg/mL or placebo, administered into the affected ear. Following the administration, subjects will rest in a supine or reclined position for 30 minutes. Study participants will have the option for a course of oral corticosteroids.
URL:
https://clinicaltrials.gov/ct2/show/NCT02809118?term=NCT02809118&rank=1

TITLE: A Phase 2b, Randomized, Double-blinded, Placebo-controlled Study to Evaluate the Safety and Efficacy of SPI-1005 to Reduce the Incidence, Severity and Duration of Acute Noise Induced Hearing Loss (NIHL)
CT.gov ID: NCT02779192
Responsible Party: Sound Pharmaceuticals, Incorporated
Target Condition(s): Noise Induced Hearing Loss
Intervention: Drug: SPI-1005 200mg, Drug: SPI-1005 400mg, Drug: Placebo
Phase: 2
Study Start Date: Feb-18
Description Provided: Randomized, double-blind, placebo-controlled, safety and efficacy study of oral SPI-1005 in adults with Noise Induced Hearing Loss (NIHL). All recruited subjects will have their severity of NIHL determined before the start of SPI-1005 treatment using otoscopy, tympanometry and audiometry. Subjects with >15 and </= 40 decibel (dB) NIHL will be enrolled and randomized to either placebo or SPI-1005. Patients will be dosed with either placebo or SPI-1005 for 7 days, beginning 1 day before an acute NIHL. Patients will have audiometry and Words In Noise Testing (WINT) before and immediately after a calibrated sound challenge (CSC). The CSC involves listening to 4 hours of pre-recorded music (100 dBA SPL) through insert earphones. The CSC induces a slight acute NIHL. Follow-up audiometry and WINT will be performed at 1 and 7 days post-CSC. A total of four clinic visits will be required over 10-14 days.
URL:
https://clinicaltrials.gov/ct2/show/NCT02779192?term=NCT02779192&rank=1

TITLE: Lidocaine Patch (Lidocaine 5%) as a Treatment for Tinnitus and Its Accompanied Symptoms
CT.gov ID: NCT02750969
Responsible Party: HaEmek Medical Center, Israel
Target Condition(s): Tinnitus
Intervention: Device: Lidoderm patch (Lidocaine 5% patch), Other: Tegaderm patch. (neutral patch, containing no drug), Procedure: blood test- serum lidocain levels, Other: Hearing tests
Phase: 4
Study Start Date: Apr-16
Description Provided: The investigators like to learn whether Lidoderm patch (lidocaine 5%) helps tinnitus patients.
so far it is known that lidocaine I.V do helps tinnitus but until now it is not clear if other means of drug delivery (e.g lidocaine patch) help tinnitus.

The investigators are going to compare 1 day of treatment with lidoderm patch cream Versus (VS.) tegaderm patch (containing no drug) in treating tinnitus patients.
URL:
https://clinicaltrials.gov/ct2/show/NCT02750969?term=NCT02750969&rank=1

TITLE: Evaluation of the Benefit of Antiviral Treatment With Valganciclovir on Congenital CMV Infection-related Deafness on Hearing and Balance
CT.gov ID: NCT02606266
Responsible Party: Assistance Publique - Hôpitaux de Paris
Target Condition(s): Congenital Cytomegalovirus (CMV)
Intervention: Drug: Valganciclovir
Phase: 2 & 3
Study Start Date: Oct-16
Description Provided: Congenital cytomegalovirus (CMV) infection is the leading cause of non-genetic neurosensory deafness and affects 0.5 to 1% of births. Twenty to thirty per cent of children will develop deafness, some of whom will progress gradually to profound bilateral deafness.
No curative treatment is currently offered for this deterioration in hearing and management involves the use of a hearing aid or cochlear implant. Many studies describe the utility of antiviral treatment on the course of the deafness. These mostly involve neonates with multi-system symptomatic forms of the infection who have been given 6 weeks of ganciclovir possibly switched to valganciclovir, which has shown benefit in stabilising auditory loss, or even improvement.
URL:
https://clinicaltrials.gov/ct2/show/NCT02606266?term=NCT02606266&rank=1

TITLE: A Three-part, Multicenter, Open Label, Single Dose Study to Assess the Safety, Tolerability, and Efficacy of Intra Labyrinthine (IL) CGF166 in Patients With Severe-to-profound Hearing Loss
CT.gov ID: NCT02132130
Responsible Party: Novartis Pharmaceuticals
Target Condition(s): Bilateral Severe to Profound Hearing Loss
Intervention: Drug: CGF166
Phase: 1 & 2
Study Start Date: Oct-14
Description Provided: The study will evaluate the safety, tolerability, and potential efficacy of CGF166 and the associated delivery procedures in patients

with severe-to-profound bilateral hearing loss. Eligible patients are required to have documented, non-fluctuating hearing loss. Part A will include a safety and tolerability cohort (N=3). Patient dosing will be staggered; dosing the next patient in a cohort will be based on a safety review of all available data through 4 weeks post-dose of the previously dosed patient(s). Part B includes a volumetric escalation design to evaluate infusion volumes of the same CGF166 concentration (5.0 x 10E11vp/mL) in 4 cohorts of patients (n=3/cohort; total of 12 patients). Part C is an expansion cohort of the highest safe and tolerable dose identified in Part B, for further assessment of efficacy.
URL:
https://clinicaltrials.gov/ct2/show/NCT02132130?term=NCT02132130&rank=1

TITLE: Comprehensive Ototoxicity Monitoring Program for VA: A Randomized Trial
CT.gov ID: NCT02099786
Responsible Party: VA Office of Research and Development
Target Condition(s): Cisplatin OtotoxicityHearing Loss
Intervention: Other: COMP-VA, Other: Standard of care, Other: Program evaluation
Phase: Not Provided
Study Start Date: Apr-15
Description Provided: Research objectives are to compare the effectiveness of ototoxicity monitoring implemented using Comp-VA or usual care with regard to (1) improving Veterans' hearing and quality of life outcomes, (2) assisting oncologists in pre-treatment counseling and therapeutic planning and (3) increasing use of post-treatment rehabilitative services.
The investigators plan to recruit a total of 320 Veterans undergoing cisplatin chemotherapeutic treatment over 4 years and 120 control subjects.
Program Evaluation: Hearing testing prior to treatment will be done in order to establish eligibility, enroll and randomize each subject into one of two study arms. At 5 weeks and at one year post-randomization hearing will be re-tested in order to obtain an estimate of longitudinal trends in hearing and quality of life assessment. Use of audiological services following treatment from the randomized subjects will be tracked. Finally, data will also be collected at each treatment interval to track use of counseling tools and oncology personnel treatment decisions.
Serial measurements from subjects receiving cisplatin prior to treatment who are randomized to:
Comp-VA group will get a screening hearing test prior to treatment, at each treatment interval and at one-month post-treatment. Auditory testing will be

done on or near the Chemo Unit and will include otoscopy, immittance testing, and a hearing testing done by the Veteran using a self-testing procedure, and may be tested using distortion product otoacoustic emissions (DPOAEs), if they cannot take a reliable hearing test.
Usual care group will receive a full audiometric evaluation (otoscopy, immittance testing, air conduction and bone conduction hearing testing, speech audiometry, and distortion product otoacoustic emissions, DPOAEs) scheduled in the audiology clinic sound booth according to Audiology Service ototoxicity monitoring protocols. Testing will be arranged according to availability of appointments and patient convenience.
Additionally data will also be collected from control subjects who are similar in age and are tested at intervals similar to the chemotherapy subjects.
URL:
https://clinicaltrials.gov/ct2/show/NCT02099786?term=NCT02099786&rank=1

TITLE: A Dose-Finding Study of N-Acetylcysteine (NAC) to Prevent Cisplatin-induced Hearing Loss in Children With Cancer
CT.gov ID: NCT02094625
Responsible Party: Children's Hospital Los Angeles
Target Condition(s): Neuroectodermal Tumors, Primitive, Liver Neoplasms, Neoplasms, Germ Cell and Embryonal, Osteosarcoma, Other Childhood Cancers Using Cisplatin-based Regimens
Intervention: Drug: N-Acetylcysteine
Phase: 1
Study Start Date: Mar-16
Description Provided: The study is a dose-finding study of N-acetylcysteine (NAC) to protect hearing in children receiving cisplatin for the treatment of their cancer. NAC also has potential to protect the kidneys from cisplatin toxicity.
The study uses a 3+3 dose-escalation scheme to determine the dose of NAC necessary to achieve serum levels consistent with hearing protection in pre-clinical animal models. Three dose levels are predefined. Once the maximum tolerated dose is determined, an expansion cohort will then be enrolled to further evaluate tolerability as well as intra-patient and inter-patient variability in achieved serum levels. An option to enroll in a separate arm for study assessments only is available for those who do not wish to receive NAC. Hearing loss in the cohort will be assessed in the entire cohort in comparison to historical and non-treated children to evaluate for trends toward efficacy.

URL:
https://clinicaltrials.gov/ct2/show/NCT02094625?cond=Neuroectodermal+Tumors%2C+Primitive%2C+Liver+Neoplasms&rank=1

TITLE: Pilot Evaluation of Combined Investigational Device: CI4CID With Controlled Dosage of Dexamethasone
CT.gov ID: NCT02905305
Responsible Party: The Hearing Cooperative Research Centre
Target Condition(s):
Intervention: Device: Contour Advance electrode with controlled dose of dexamethasone base, Device: Contour Advance electrode
Phase: Not Provided
Study Start Date: Dec-13
Description Provided: In an effort to further preserve residual acoustic hearing after cochlear implantation, it may be beneficial to incorporate anti-inflammatory agents into the electrode array for passive elution over a time course after implantation. This study aims to assess the ease and effectiveness of such an electrode design, and to assess the preliminary safety of use of such a device in the post-operative period. This study is a first-time-in-human study of the investigational device.
In the first instance, the aim of the current investigation is to obtain first experience in use of a Combined Device in the adult clinical population, and to assess tools and techniques that may be considered in future clinical studies of similar devices.
URL:
https://clinicaltrials.gov/ct2/show/NCT02905305?term=NCT02905305&rank=1

TITLE: An Open-Label Study to Determine the Long-Term Safety, Tolerability and Biological Activity of UshStat® in Patients With Usher Syndrome Type 1B
CT.gov ID: NCT02065011
Responsible Party: Sanofi
Target Condition(s): Usher Syndrome
Intervention: Drug: UshStat
Phase: 1 & 2
Study Start Date: Sep-13
Description Provided: Primary Objective: To evaluate the long-term safety and tolerability of UshStat® in patients with Usher syndrome type 1B

Secondary Objective: To assess long-term safety and biological activity of UshStat®
URL:
https://clinicaltrials.gov/ct2/show/NCT02065011?term=NCT02065011&rank=1

TITLE: Efficacy and Safety of AM-101 in the Treatment of Acute Peripheral Tinnitus 3
CT.gov ID: NCT02040194
Responsible Party: Auris Medical AG
Target Condition(s): Tinnitus
Intervention: Drug: AM-101, Drug: Placebo
Phase: 3
Study Start Date: Jan-14
Description Provided: This phase III study is assessing the drug's safety and is aiming to demonstrate efficacy of repeated intratymanic AM-101 injections in the treatment of acute peripheral tinnitus (up to 3 months (Stratum A), or between >3 and 6 months (Stratum B) from onset).
URL:
https://clinicaltrials.gov/ct2/show/NCT02040194?term=NCT02040194&rank=1

TITLE: A Randomized, Double Blind, Placebo-controlled, Parallel Group Study to Determine the Efficacy, the Duration of Action, and Safety of Latanoprost in Patients With Menière's Disease
CT.gov ID: NCT01973114
Responsible Party: Synphora AB
Target Condition(s): Menière's Disease
Intervention: Drug: Latanoprost, Other: Placebo
Phase: 2
Study Start Date: Oct-13
Description Provided: The purpose of the study is to evaluate the dose regimen, efficacy and safety of latanoprost for the treatment of Menière's disease.
URL:
https://clinicaltrials.gov/ct2/show/NCT01973114?term=NCT01973114&rank=1

TITLE: Double-blind, Randomized, Placebo-controlled Study on Efficacy, Safety and Tolerability of Ancrod in Patients With Sudden Sensorineural Hearing Loss (SSHL)
CT.gov ID: NCT01621256
Responsible Party: Nordmark Arzneimittel GmbH & Co. KG

Target Condition(s): Hearing Loss, Deafness, Hearing Loss, Sensorineural, Hearing Disorders, Ear Diseases
Intervention: Drug: Ancrod, Drug: Saline solution
Phase: 1 & 2
Study Start Date: May-13
Description Provided: The purpose of this study is to determine whether ancrod is effective and safe in the treatment of sudden sensorineural hearing loss (SSHL).
URL:
https://clinicaltrials.gov/ct2/show/NCT01621256?term=NCT01621256&rank=1

TITLE: Safety and Efficacy Study of SPI-1005 for Prevention of Chemotherapy Induced Hearing Loss
CT.gov ID: NCT01451853
Responsible Party: Sound Pharmaceuticals, Incorporated
Target Condition(s): Lung Cancer, Head and Neck Cancer, Hearing Loss, Ototoxicity, Tinnitus, Neuropathy
Intervention: Drug: SPI-1005 Low Dose, Drug: SPI-1005 Middle Dose, Drug: SPI-1005 High Dose, Drug: Placebo
Phase: 2
Study Start Date: Jan-18
Description Provided: Chemotherapy treatment with the platinum containing chemotherapies (e.g. cisplatin, carboplatin) are well noted and studied for their ability to cause ototoxicity which includes hearing loss, tinnitus, vertigo, or dizziness. It is the objective of this study to determine the safety and efficacy of SPI-1005 at three dose levels when delivered orally twice daily for 3 days, surrounding each cycle of platinum chemotherapy for head and neck or non-small cell lung cancer patients to prevent and treat chemotherapy induced hearing loss and tinnitus.
SPI-1005, a proprietary oral formulation of ebselen is a small molecule mimic and inducer of the enzyme Glutathione Peroxidase. GPx reduces reactive oxygen species (ROS) by reacting with glutathione. SPI-1005 has been shown to reduce cisplatin induced hearing threshold shift in animal studies.
URL:
https://clinicaltrials.gov/ct2/show/NCT01451853?term=NCT01451853&rank=1

TITLE: Double Blind, Placebo-controlled, Randomized Clinical Trial to Evaluate the Efficacy and Safety of a Transtympanic Treatment of Tinnitus With Caroverine
CT.gov ID: NCT01174979
Responsible Party: Phafag AG

Target Condition(s): Tinnitus
Intervention: Drug: Caroverin
Phase: 3
Study Start Date: Jan-11
Description Provided: This trial is a randomized, double blind, placebo controlled study on patients suffering from inner ear diseases with tinnitus as a principal symptom. The study will investigate the transtympanic treatment with a 1,5 % caroverine solution. Each patient will undergo treatment for 2 cycles of 48 hours each.
URL:
https://clinicaltrials.gov/ct2/show/NCT01174979?term=NCT01174979&rank=1

https://hearing.health.mil/Research/PIHL-Working-Group/PIHL-Newsletters

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