Title

Prevention of cisplatin-induced hearing loss by extended release fluticasone propionate intracochlear implants

Authors

Pierstorff, Erik
Yang, Wan-Wan
Chen, Yen-Jung Angel
et al.

Publication Date

2019-06-01

DOI

10.1016/j.ijporl.2019.03.021

Peer reviewed

HHS Public Access

Author manuscript

Int J Pediatr Otorhinolaryngol. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

Int J Pediatr Otorhinolaryngol. 2019 June ; 121: 157–163. doi:10.1016/j.ijporl.2019.03.021.

Prevention of cisplatin-induced hearing loss by extended release fluticasone propionate intracochlear implants

Erik Pierstorff[a], **Wan-Wan Yang**[a], **Yen-Jung Angel Chen**[b], **Shirley Cheung**[a], **Federico Kalinec**[b], and **William H. Slattery**[a]

[a]O-Ray Pharma, Inc., 2285 E. Foothill Blvd, Pasadena, CA 91107

[b]Department of Head and Neck Surgery, David Geffen School of Medicine at UCLA. 10833 Le Conte Ave., Los Angeles, CA 90095

Abstract

Objective: Cisplatin is a chemotherapeutic drug known to induce hearing loss. Although corticosteroids may help to mitigate the ototoxic side effects of cisplatin, there are complications associated with their systemic and prolonged use. The goal of this study is to test the efficacy of extended-release fluticasone propionate intracochlear implant particles to protect against cisplatin-induced hearing loss.

Methods: We used guinea pigs (n=9) injected with cisplatin (IP, 12 mg/kg weight). Fluticasone particles were delivered to the cochlear scala tympani through the round window membrane into the right ears of the guinea pigs (left ears being used as a control) two weeks prior to cisplatin administration, and hearing function was evaluated by ABR and DPOAE before implantation, immediately before cisplatin administration, and 2 weeks after the challenge with cisplatin. Data was statistically evaluated using paired *t* test analysis.

Results: No significant differences were observed in ABR threshold between control and implanted ears on day 14 (23.9±2.3 dB vs. 25.6±1.3 dB, P=0.524), whereas the significant cisplatin-induced hearing loss in control animals (23.9±2.3 dB at day 14 vs. 40.7±2.5 dB at day 28, P≤0.0001) was prevented in implanted animals (25.6±1.3 dB at day 14 vs. 25.0±3.1 at day 28, P≥0.85). A similar, though not statistically significant, trend was observed in DPOAE responses in untreated ears (7.9±5.8 dB at day14 vs. −0.5±5.3 dB at day 28, P=0.654) as compared to treatment (11.1±3.4 dB at day 14 vs. 13.6±4.8 dB at day 28, P= 0.733).

Conclusion: These results suggest that fluticasone intracochlear implants are safe and able to provide effective otoprotection against cisplatin-induced hearing loss in the guinea pig model.

Corresponding author: Erik Pierstorff, epierstorff@oraypharma.com; +1 (626) 844-1906; 2285 E. Foothill Blvd, Pasadena, CA 91107, United States.

Declaration of Interests

E.P. and W.S. own stock in O-Ray Pharma.

Keywords

Cochlea; Cisplatin; Corticosteroids; Ototoxicity; Implantation

1. Introduction

Cisplatin is a potent anti-neoplastic agent frequently used in the clinic for the treatment of a variety of solid tumors, such as ovarian, testicular, cervical, lung, head, neck and bladder cancers. Its administration, however, is commonly associated with severe nephrotoxicity, peripheral neuropathy, and ototoxicity [1]. The Royal National Institute for Deaf People's 2005 Ototoxicity and Otoprotective Agents Market Report estimated that 700,000 new cancer patients in the United States and Western Europe receive cisplatin chemotherapy each year. This patient number increases to about 1 million when including those receiving cisplatin for advanced or recurrent cancer.

Studies have shown that increasing doses of cisplatin are correlated with increasing loss of outer hair cells (OHC), one of the two types of auditory sensory cells together with inner hair cells (IHC), leading to irreversible hearing loss [2–5]. This side effect of cisplatin is especially pronounced in young children, with a tremendous impact on speech, cognitive, and social development [6, 7]. The symptoms associated with ototoxicity in children may occur within hours after cisplatin administration; however, delayed ototoxicity can also occur years after [8]. Recent studies have shown that cisplatin is retained in the tissues of the inner ear of mice and humans for much longer periods than was previously thought, with cisplatin detected months to years after the last administration [9]. Currently, no regulatory approved drug-based therapy for the prevention or treatment of cisplatin's ototoxic side effects is available. Based on the long-term retention of cisplatin in the inner ear, any approved medication should either prevent passage of cisplatin into the inner ear or have the capability to continually protect against ototoxicity for months to years. In a previous study [10], we described an extended-release fluticasone propionate particle formulation, termed OR-102, developed for direct implantation into the cochlea. Moreover, we demonstrated that individual OR-102 particles can release fluticasone propionate inside the cochlear for up to six months, and ears receiving the implanted particle exhibited no changes in hearing function when compared to control ears [10].

The purpose of this study was to determine the *in vivo* efficacy of the extended-release fluticasone propionate particle OR-102 for cisplatin-induced hearing loss using a guinea pig model. This has the dual purpose of demonstrating the retention of drug activity through manufacture and drug release *in vivo* as well as validating the protective activity of fluticasone against cisplatin-dependent hearing loss.

2. Materials and Methods

2.1 Animals

Young albino guinea pigs (Cavia porcellus, 200–300 g, n=9) were used for intracochlear implantation experiments, with all experimental procedures approved by the House Ear Institute Institutional Animal Care and Use Committee (approval number #HE1121-10-11).

2.2 Production of extended release fluticasone propionate particles

USP Fluticasone propionate was purchased from Molcan Corporation, Ontario, Canada. The polymer used in this study is a thermally modified polyvinyl alcohol to produce the final extended release fluticasone propionate particle (OR-102) [10]. Particle batches were size fractionated via sieving with a 180 μm sieve to enrich for the desired size ranges. Batch release was performed using sieved particles. Parameters for size/shape of particles and the correlation with drug load were performed to establish criteria for particle selection. Fluticasone propionate particles 45–212 μm in size were selected for PVA coating. PVA was cross-linked via heat treatment for a 100+ day release time-frame. Particles were run through a selection criteria in order to obtain similar particles for each study. Particles were visualized using light microscopy. Particle length and diameter were measured with a graticule and accepted only if they fell within a specific range. Accepted particles were cylindrical/hexagonal in shape. Drug crystal integrity was examined to eliminate any particles with cracks along the length and particle topography was assessed for the presence of smaller attached particles, crystals or polymer masses. Any imperfections were cause for rejection.

2.3 Scanning electron microscopy (SEM)

The surface topography of the OR-102 particles was investigated by Scanning Electron Microscopy using an XL 30 S FEG operating at 5kVa (FEI Inc, Hillsboro, OR). Analysis of the coated OR-102 particles' surface showed complete coating of the drug crystals. Moderate agglomeration of polymer was observed in some samples. Substantial agglomeration of polymer can occlude the particle surface and impede drug release. However, the level of occlusion was generally minimal. Particle selection criteria mentioned above were developed to select particles with little or no polymer agglomeration on the surface. (Figure 1)

2.4 *In vivo* implantation of extended release fluticasone particles

OR-102 particles were selected based on size, shape, and results of topographical analysis via SEM imaging as described above. These particles were used in these studies and implanted into the cochleae of healthy albino guinea pigs prior to challenging the animals with cisplatin (Figure 2).

Guinea pigs received a single OR-102 implant particle through the round window membrane into the scala tympani of their right ears, with their left ears being used as a control. Under general anesthesia, a postauricular incision was made over the bulla in the experimental ear. A small hole was drilled through the bulla using a posterior approach and small pieces of bone were chipped away until the RWM was clearly visible and accessible (Figure 3). Next,

the ear was positioned with the round window facing horizontally and superiorly, a 32-gauge needle was used to puncture the round window, and the OR-102 particle was placed in contact with the perilymph in the scala tympani. A drop of sodium hyaluronate was placed over the round window injection site to avoid leakage of perilymphatic fluids. A suture was used to close the wound.

2.5 Cisplatin Administration

Cisplatin was administered to guinea pigs via a single intraperitoneal injection, at a concentration of 12 mg/kg, 14 days after intracochlear implantation of OR-102.

2.6 Auditory Measurements

Animals were anesthetized for auditory testing. Hearing was tested pre-implant, 14, and 28 days post-implant. Auditory Brainstem Responses (ABRs) were measured under computer control in response to clicks 50 μs in duration from levels below threshold to 80 dB SPL in 5 dB steps. Responses were detected with subcutaneous needle electrodes placed at the vertex and ventrolateral to the left and right pinna. Response was amplified (10,000 times), filtered (0.1–3 kHz bandpass), and averaged (across 512 sweeps at each frequency-level combination). On visual inspection of stacked waveforms, “threshold” was defined as the lowest stimulus level at which response peaks are present. These visual detection threshold judgments were confirmed following termination of the experiment by offline display and analysis of the stored waveforms. DPOAE (2f1 – f2) Input/output functions were recorded. Response amplitude was recorded as a function of L2 (L1 – L2 = 10dB); primaries were incremented together in 5 dB steps (from 20 to 80 dB SPL) spanning the frequency range f2 = 5.6 – 45.2 kHz (f2/f1 = 1.2). Ear-canal sound pressures were amplified, digitally sampled, averaged until a SNR of 6dB is achieved. DPOAE level at 2f1 – f2 and surrounding noise floor values (±50 Hz of 2f1 – f2) were extracted. DPOAE data was compared with ABR data at corresponding frequencies. Responses were recorded at baseline (before surgical exposure of the bulla), after introduction of the particle, and prior to sacrifice.

2.7. Statistical Analysis

Data was statistically analyzed via paired *t* tests utilizing GraphPad QuickCalcs software (www.graphpad.com).

3. Results:

Hearing assessments via auditory brainstem response (ABR) were performed before implantation of OR-102 (pre-op day 1), pre-cisplatin administration (14 days after implantation), and 14 days after cisplatin administration (28 days after implantation). ABR results (mean±SEM) are depicted in Figure 4. No significant differences were observed in ABR threshold between control (non-implanted) and OR-102 implanted ears on day 14 (compare pre-cisplatin day 14, No Surgery and Implant ABR values: 23.9±2.3 dB vs. 25.6±1.3 dB, P=0.524). However, a small but significant elevation in ABR threshold was observed in implant ears between pre-op day 1, and pre-cisplatin day 14 (compare OR-102 implant ears pre-op day 1 and pre-cisplatin day 14: 19.4±1.3 dB vs. 25.6±1.3 dB, P=0.0158). This small elevation in ABR threshold may be due to the surgical intervention. No

statistically significant differences were observed in ABR threshold in control ears between pre-op day 1, and pre-cisplatin day 14 (compare control ears pre-op day 1 and pre-cisplatin day 14: 22.8±1.2 dB vs. 23.9±2.3 dB, P=0.695).

In contrast, statistically significant hearing loss was observed in the control ears following cisplatin treatment (compare pre-cisplatin day 14, and post-cisplatin day 28: 23.9±2.3 dB vs. 40.7±2.5 dB, P≤0.0001). Importantly, no significant differences were observed in ABR threshold between ears implanted with OR-102 when comparing pre-cisplatin day 14, and post-cisplatin administration (compare day 28: 25.6±1.3 dB vs. 25.0±3.1 dB, P≥0.85). These results suggest that OR-102 particles prevent cisplatin-induced hearing loss (Figure 4).

Distortion product otoacoustic emissions (DPOAE) were also monitored in all conditions tested (Figure 5). In most circumstances, there was no statistically significant difference in DPOAE measurements. This may be due to the small sample size and/or large variability in readings from the DPOAE testing method. However, there is an apparent trend observed suggesting that cisplatin impairs hearing and that the implantation of OR-102 extended release fluticasone particles. Specific results are as follows. There was no statistically significant difference between control and implant groups between pre-cisplatin day 14, and post-cisplatin day 28 (control ears: compare pre-cisplatin day 14, and post-cisplatin day 28: 7.9±5.8 dB vs. −0.5±5.3 dB, P=0.654; OR-102 treatment: compare pre-cisplatin day 14, and post-cisplatin day 28: 11.1±3.4 dB vs. 13.6±4.8 dB, P= 0.733). There was also no statistically significant difference between control and implant ears at post-cisplatin day 28 (compare control and implant ears, post-cisplatin day 28: 0.5±5.3 vs 13.6±4.8, P=0.120). Additionally, there was no statistically significant difference in the OR-102 implant ear between pre-surgery day 1, and pre-cisplatin day 14 (compare implant ears, pre-op day 1, and pre-cisplatin day 14: 14.5±4.5 vs 11.1±3.4, P= 0.572). However, a statistically significant difference was observed in control ears between day 1 and day 14 (compare control ears, pre-op day 1, and pre-cisplatin day 14: 15.0±4.6 vs 7.9±5.8, P=0.018).

4. Discussion:

Our results suggest the efficacy of fluticasone propionate implants delivered directly into the cochlea in the prevention of cisplatin-dependent hearing loss for over a course of four weeks.

4.1 Cisplatin and ototoxicity

Cisplatin is the chemotherapeutic agent of choice for the treatment of a variety of solid tumors because of its ability to interfere with DNA replication in cancerous cells. Cisplatin is commonly used for the treatment of medulloblastoma, neuroblastoma, osteosarcoma, testicular, ovarian, cervical, bladder, lung, and head and neck cancers [11]. However, cisplatin also interferes with DNA replication in healthy cells, and it can induce cell death by different mechanisms even in non-dividing cells, such as OHCs and IHCs.

Cisplatin ototoxicity is characterized by progressive, bilateral and irreversible hearing loss, preferentially affecting high frequencies [12]. Cisplatin affects mainly OHCs, although IHCs, spiral ganglion neurons and stria vascularis cells are also major targets, by generating

ROS and activating inflammatory cytokines and stress signaling pathways [13, 14]. These events eventually lead to cell death, mostly via induction of apoptosis [13]. The loss of OHCs from systemic administration of cisplatin correlates directly with the severity of hearing loss and is thought to be the cause of cisplatin-dependent damage to hearing. Young children are especially vulnerable to this ototoxic side effect of cisplatin. As recent studies demonstrated, cisplatin is retained in the tissue of the inner ear for weeks to months following administration [9]. There are currently no approved medications for cisplatin's ototoxic side effects and any newly developed otoprotectant would need to be present for the full duration of cisplatin's residency in the inner ear. The development of an otoprotective treatment would have significant impacts on patient quality of life.

4.2 Prevention of cisplatin-based hearing loss

Various compounds have been investigated as potential protective agents against the side effects of cisplatin chemotherapy, including antioxidants [15, 16], neurotrophins [17, 18], sulfur-containing nucleophiles [19], and corticosteroids [20, 21]; other oral formulations are currently in clinical trials. However, there is the risk that the high levels of systemic drug required for otoprotection may decrease the effectiveness of the cisplatin chemotherapy at its intended target. As such, different strategies for delivery of otoprotective agents have been attempted. One technique is intratympanic injections to locally administer the protective agent [20–23]. Other techniques include timing the administration of systemic dosing of the protective agent such that it does not disrupt chemotherapy function but retains otoprotective activity [24]. The efficacy of these treatment options continues to be tested in preclinical and clinical settings.

4.3 Extended release fluticasone formulation

Systemic administration of drug requires the agent to cross the blood labyrinth barrier (BLB) to reach the inner ear [25, 26]. However, because only a small amount of drug is able to cross the BLB, high doses of medication must be administered to achieve the appropriate drug concentration and to have a therapeutic effect in the cochlea. Furthermore, there are numerous negative side effects associated with the systemic administration of drugs such as corticosteroids. Although the intratympanic administration of pharmacological agents has been used widely over the past few decades for the treatment of middle ear indications [27–32], the drug must be retained in the middle ear cavity and in contact with the round window membrane or the annular ligament of the oval window for a sufficient amount of time in order to deliver drug to the cochlea [28, 33]. Yet, drugs administered to the middle ear cavity have been shown to quickly discharge into the Eustachian tube via mucociliary flow [34, 35]. Increasing the frequency of drug administration to compensate for this issue increases the cost of therapy, the risk of tympanic membrane perforations [36], and the risk of infection during the procedure [27]. Therefore, intracochlear drug delivery systems have been developed to allow for improved dosing control and reduced drug concentration gradients [37–40].

Corticosteroids remain attractive candidates for treating various inner ear indications, including cisplatin-dependent hearing loss, as they have been studied extensively and are well-characterized. With their anti-inflammatory, vasodilating, and immunosuppressive

effects, corticosteroids are commonly used for the management of inner ear disorders such as Meniere's disease, autoimmune inner ear disease, and certain vestibular conditions. The published literature suggests that the major advantage of topical steroid administration is in their ability to achieve high local drug levels without the high systemic levels that cause side effects [41].

Oral corticosteroids are not used clinically to prevent ototoxicity due to the high dosage required and the complications associated with their long-term use. Furthermore, it is possible that systemic corticosteroids could decrease the anti-cancer activity of cisplatin. A study by Herr et al. has shown that systemic administration of dexamethasone, another corticosteroid, downregulates apoptotic genes in carcinogenic cells [42]. Therefore, the local administration of corticosteroids can greatly enhance the efficacy of the drug as well as significantly decrease the side effects of systemic corticosteroid administration. Intratympanic injections of therapeutics can enhance uptake of drugs into the inner ear while decreasing systemic exposure. However, variabilities of the anatomy of the inner ear can make accurate dosing difficult from patient to patient. The development of a corticosteroid drug delivery system for intracochlear implantation can overcome these limitations of systemic and intratympanic corticosteroid administration.

Devices such as the Norplant® [43] and the Vitrasert® [44] are membrane-based drug delivery platforms that can permit linear/pseudo-zero order drug delivery over a period of months. The Vitrasert® implant is usually placed into the eye with a single implantation. This membrane-based approach has additionally allowed researchers to deliver corticosteroids to the eyes of animals for up to three years from a single implantation [45] and is currently FDA approved for patients with chronic noninfectious uveitis [46]. Thus, patients can constantly be treated for symptoms for three years with a single implantation event.

Previously, our group demonstrated the pharmacokinetics and safety of an extended-release fluticasone propionate particle formulation implanted directly into the cochlea of an animal model, demonstrating drug release for up to a six-month time period [10]. In the present study, we utilized the extended-release fluticasone particles to mitigate the ototoxicity caused by cisplatin in a guinea pig model. The results of this study demonstrate the release of active drug over a course of at least four weeks as measured by protection against cisplatin-based ototoxicity for at least four weeks after implantation. A major advantage of the extended-release drug delivery technology investigated here is that it reduces or eliminates the burst release of drug and can maintain steady drug release over the duration of months or years. Previous studies with these extended-release fluticasone particles have demonstrated release profiles for at least three months. Thus, a single procedure to implant an intracochlear extended-release fluticasone propionate particle could protect against cisplatin-based ototoxicity for at least three months.

4.4 OR-102 Protection Against Cisplatin Ototoxicity

The OR-102 extended release fluticasone particles were tested for their ability to protect against cisplatin-dependent ototoxicity. Auditory brainstem response (ABR) results show that when animals are challenged with cisplatin, ears implanted with OR-102 exhibit

statistically significantly better hearing when compared to control ears. This suggests the efficacy of OR-102 in the prevention of cisplatin-dependent hearing loss. A slight, but statistically significant elevation in ABR threshold is observed in implanted ears between day 1 (pre-implantation) and day 14 (pre-cisplatin). This may be due to the surgical procedure. However, as reported previously by our group, the surgical technique and implantation of OR-102 particles can be performed with little or no damage to hearing. Distortion product otoacoustic emissions (DPOAE) were also measured and an apparent trend corroborating ABR data results is observed. However, this apparent trend in DPOAE results was not considered statistically significant. The lack of statistical significance may be due to the high level of variability in DPOAE results and/or the small sample size. Additional animals would need to be tested to determine if DPOAE results may actually corroborate ABR results.

The OR-102 particles used in these studies are comprised of a solid drug core encapsulated by a thin layer of polyvinyl alcohol (PVA) polymer to control the release of the encapsulated drug. PVA is a synthetic polymer derived from polyvinyl acetate and is known for its biocompatibility and chemical resistance [47]. With its extensive safety profile over the decades, PVA has proven to be a reliable polymer in medical devices and as a coating agent for pharmaceutical agents without affecting the device or drug being delivered through it [47–49]. It is unlikely that the PVA component of the OR-102 particle has any effect on cisplatin or cisplatin-mediated ototoxicity. Each OR-102 pellet contains ~300pg of cross-linked PVA which is biostable and is not expected to break down over a 4-week period. This small amount of material would have limited access and interaction with cisplatin in the inner ear. Additionally, multiple PVA-based cisplatin drug delivery systems have been developed that use PVA as a polymer in their shells or hydrogels [50–55]. These extended-release cisplatin systems have demonstrated that the use of PVA as a component did not sequester the chemotherapeutic effects of cisplatin, and instead, showed that the PVA controlled the release of cisplatin *in vivo* [50, 51]. These previous studies using PVA-based cisplatin drug delivery systems suggest that the PVA in OR-102 would not sequester the chemotherapeutic properties of cisplatin *in vivo*.

The use of experimental placebos is particularly indicated to investigate whether a given pharmacological drug is effective, per se, or if its apparent beneficial effect is linked to a psychological and/or other unknown mechanism/s. Corticosteroids like fluticasone, however, have been extensively investigated, and there are no doubts about their efficacy in preventing cisplatin-induced hearing loss. As mentioned above, one major problem with using corticosteroids is the well described side effects associated with systemic approaches. This is the issue that we try to tackle with our therapeutic approach using intracochlear delivery of the drugs.

In our previous work [10] we described the pharmacokinetics of the fluticasone released by the OR-102 intracochlear implant. Since the goal of the present study is to demonstrate that the fluticasone released by the implant is still effective in preventing cisplatin-induced hearing loss and not to investigate whether the implant itself may contribute to this effect, we saw no reason to use placebos.

5. Conclusion:

Corticosteroids, such as fluticasone propionate, have been used extensively for a variety of inner ear disorders. In this study, our group has developed an extended-release fluticasone propionate particle formulation (OR-102) to mitigate cisplatin-induced hearing loss. The local administration of drug into the inner ear can reduce the potential for systemic side effects of steroid administration while eliminating the possibility of disrupting cisplatin activity against carcinogenic cells in the rest of the body. The addition of OR-102 was shown to protect against cisplatin-induced hearing loss over a course of four weeks. ABR threshold results show no significant difference in OR-102 treated ears following cisplatin treatment while untreated ears demonstrated significant cisplatin-dependent hearing loss. These results suggest implantation of extended-release steroid particles (OR-102) in the cochlea protects from cisplatin-induced hearing damage in a guinea pig model in a safely manner. Additional safety studies may be required on the particles and surgical technique before clinical potential can be fully ascertained. In addition to cisplatin-dependent hearing loss, the potential exists to utilize OR-102 to treat a variety of inner ear disorders that are responsive to long-term steroid treatment (i.e. autoimmune inner ear disease). Although intracochlear implantation is more invasive than intratympanic injection, we believe that procedures can be developed to safely and reproducibly implant particles into the cochlea with little risk of hearing damage or infection.

Acknowledgements

This study was supported, in part, by NIDCD Grant: 5R44DC008477 to EP and WHS.

References

[1]. Johnstone TC, Suntharalingam K, Lippard SJ, The Next Generation of Platinum Drugs: Targeted Pt(II) Agents, Nanoparticle Delivery and Pt(IV) Prodrugs. Chem Rev. 116(5) (2016) 3436–3486. [PubMed: 26865551]

[2]. Trzaska S, Cisplatin. Chemical & Engineering News. 83(25) (2005).

[3]. Frisina RD, Wheeler HE, Fossa SD, Kerns SL, Fung C, Sesso HD, Monahan PO, Feldman DR, Hamilton R, Vaughn DJ, Beard CJ, Budnick A, Johnson EM, Ardeshir-Rouhani-Fard S, Einhorn LH, Lipshultz SE, Dolan ME, Travis LB, Comprehensive Audiometric Analysis of Hearing Impairment and Tinnitus After Cisplatin-Based Chemotherapy in Survivors of Adult-Onset Cancer. J Clin Oncol. 34(23) (2016) 2712–20. [PubMed: 27354478]

[4]. Kopelman J, Budnick AS, Sessions RB, Kramer MB, Wong GY, Ototoxicity of high-dose cisplatin by bolus administration in patients with advanced cancers and normal hearing. Laryngoscope. 98(8 Pt 1) (1988) 858–64. [PubMed: 3398663]

[5]. Bokemeyer C, Berger CC, Hartmann JT, Kollmannsberger C, Schmoll HJ, Kuczyk MA, Kanz L, Analysis of risk factors for cisplatin-induced otoxocity in patients with testicular cancer. Br J Cancer. 77(8) (1998) 1355–1362. [PubMed: 9579846]

[6]. Allen GC, Tiu C, Koike K, Ritchey AK, Kurs-Lasky M, Wax MK, Transient-evoked otoacoustic emissions in children after cisplatin chemotherapy. Otolaryngol Head Neck Surg. 118(5) (1998) 584–8. [PubMed: 9591854]

[7]. Li Y, Womer RB, Silber JH, Predicting cisplatin ototoxicity in children: the influence of age and the cumulative dose. Eur J Cancer. 40(16) (2004) 2445–51. [PubMed: 15519518]

[8]. Knight KR, Kraemer DF, Neuwelt EA, Ototoxicity in children receiving platinum chemotherapy: underestimating a commonly occurring toxicity that may influence academic and social development. J Clin Oncol. 23(34) (2005) 8588–96. [PubMed: 16314621]

[9]. Bertolini P, Lassalle M, Mercier G, Raquin MA, Izzi G, Corradini N, Hartmann O, Platinum compound-related ototoxicity in children: long-term follow-up reveals continuous worsening of hearing loss. J Pediatr Hematol Oncol. 26(10) (2004) 649–55.

[10]. Breglio AM, Rusheen AE, Shide ED, Fernandez KA, Spielbauer KK, McLachlin KM, Hall MD, Amable L, Cunningham LL, Cisplatin is retained in the cochlear indefinitely following chemotherapy. Nature Com. 11 21;8(1) (2017) 1654 DOI: 10.1038/s41467-017-01837-1

[11]. Pierstorff E, Chen S, Chaparro MP, Cortez JM Jr, Chen YJ, Ryu SY, Tsai SM, Baum MM, Yang WW, Kalinec F, Smith T, Ludwig S, Slattery WH, A Polymer-Based Extended Release System for Stable, Long-term, Intracochlear Drug Delivery. Otol Neurotol. 39(9) (2018) 1195–1202. [PubMed: 30199502]

[12]. Rybak LP, Whitworth CA, Ototoxicity: therapeutic opportunities. Drug Discov Today. 10(19) (2005) 1313–21. [PubMed: 16214676]

[13]. Nakai Y, Konishi K, Chang KC, Ohashi K, Morisaki N, Minowa Y, Morimoto A, Ototoxicity of the anticancer drug cisplatin. An experimental study. Acta Otolaryngol 93(1–6) (1982) 227–32. [PubMed: 7199807]

[14]. Boulikas T, Vougiouka M, Cisplatin and platinum drugs at the molecular level. (Review). Oncol Rep. 10(6) (2003) 1663–82. [PubMed: 14534679]

[15]. Rybak LP, Mechanisms of cisplatin ototoxicity and progress in otoprotection. Curr Opin Otolaryngol Head Neck Surg. 15(5) (2007) 364–9. Epub 2007/09/08. doi: 10.1097/MOO.0b013e3282eee45200020840-200710000-00014 [pii]. [PubMed: 17823555]

[16]. Dickey DT, Muldoon LL, Kraemer DF, Neuwelt EA, Protection against cisplatin-induced ototoxicity by N-acetylcysteine in a rat model. Hear Res. 193(1–2) (2004) 25–30. [PubMed: 15219317]

[17]. Choe WT, Chinosornvatana N, Chang KW, Prevention of cisplatin ototoxicity using transtympanic N-acetylcysteine and lactate. Otol Neurotol. 25(6) (2004) 910–5. [PubMed: 15547419]

[18]. Chen X, Frisina RD, Bowers WJ, Frisina DR, Federoff HJ, HSV amplicon-mediated neurotrophin-3 expression protects murine spiral ganglion neurons from cisplatin-induced damage. Mol Ther. 3(6) (2001) 958–63. [PubMed: 11407910]

[19]. Meen E, Blakley B, Quddusi T, Brain-derived nerve growth factor in the treatment of sensorineural hearing loss. Laryngoscope. 119(8) (2009) 1590–3. [PubMed: 19479743]

[20]. Videhult P, Laurell G, Wallin I, Ehrsson H, Kinetics of Cisplatin and its monohydrated complex with sulfur-containing compounds designed for local otoprotective administration. Exp Biol Med (Maywood). 231(10) (2006) 1638–45. [PubMed: 17060685]

[21]. Daldal A, Odabasi O, Serbetcioglu B, The protective effect of intratympanic dexamethasone on cisplatin-induced ototoxicity in guinea pigs. Otolaryngol Head Neck Surg. 137(5) (2007) 747–52. [PubMed: 17967639]

[22]. Hill GW, Morest DK, Parham K, Cisplatin-Induced Ototoxicity: Effect of Intratympanic Dexamethasone Injections. Otol Neurotol. 29(7) (2008) 1005–1011. [PubMed: 18716567]

[23]. Topdag M, Iseri M, Gelenli E, Yardimoglu M, Yazir Y, Ulubil SA, Topdag DO, Ustundag E, Effect of intratympanic dexamethasone, memantine and piracetam on cellular apoptosis due to cisplatin ototoxicity. J Laryngol Otol. 126(11) (2012) 1091–6. [PubMed: 22947376]

[24]. Shafik AG, Elkabarity RH, Thabet MT, Soliman NB, Kalleny NK, Effect of intratympanic dexamethasone administration on cisplatin-induced ototoxicity in adult guinea pigs. Auris Nasus Larynx. 40(1) (2013) 51–60. [PubMed: 22884636]

[25]. Freyer DR, Chen L, Krailo MD, Knight K, Villaluna D, Bliss B, Pollock BH, Ramdas J, Lange B, Van Hoff D, VanSoelen ML, Wiernikowski J, Neuwelt EA, Sung L, Effects of sodium thiosulfate versus observation on development of cisplatin-induced hearing loss in children with cancer (ACCL0431): a multicenter, randomised, controlled, open label, phase 3 trial. Oncology. 18(1) (2017) 63–74.

[26]. Karasawa T, Steyger PS, An integrated view of cisplatin-induced nephrotoxicity and ototoxicity. Toxicol Lett. 237(3) (2015) 219–27. [PubMed: 26101797]

[27]. Juhn SK, Rybak LP, Fowlks WL, Transport characteristics of the blood--perilymph barrier. Am J Otolaryngol. 3(6) (1982) 392–6. [PubMed: 6297328]

[28]. Slattery WH, Fisher LM, Iqbal Z, Friedman RA, Liu N, Intratympanic steroid injection for treatment of idiopathic sudden hearing loss. Otolaryngol Head Neck Surg. 133(2) (2005) 251–9. [PubMed: 16087024]

[29]. McCall AA, Swan EE, Borenstein JT, Sewell WF, Kujawa SG, McKenna MJ, Drug delivery for treatment of inner ear disease: current state of knowledge. Ear Hear. 31(2) (2010) 156–65. [PubMed: 19952751]

[30]. Salt AN, Plontke SK, Principles of local drug delivery to the inner ear. Audiol Neurootol. 14(6) (2009) 350–60. [PubMed: 19923805]

[31]. Plontke SK, Biegner T, Kammerer B, Delabar U, Salt AN, Dexamethasone concentration gradients along scala tympani after application to the round window membrane. Otol Neurotol. 29(3) (2008) 401–6. [PubMed: 18277312]

[32]. Stachler RJ, Chandrasekhar SS, Archer SM, Rosenfeld RM, Schwartz SR, Barrs DM, Brown SR, Fife TD, Ford P, Ganiats TG, Hollingsworth DB, Lewandowski CA, Montano JJ, Saunders JE, Tucci DL, Valente M, Warren BE, Yaremchuk K, Robertson PJ; American Academy of Otolaryngology-Head and Neck Surgery, Clinical practice guideline: sudden hearing loss. Otolaryngol Head Neck Surg. 146(3 Suppl) (2012) S1–35. [PubMed: 22383545]

[33]. Sajjadi H, Paparella MM, Meniere's disease. Lancet. 372(9636) (2008) 406–14. [PubMed: 18675691]

[34]. Clark G, The multi-channel cochlear implant: past, present and future perspectives. Cochlear Implants Int. 10 Suppl 1 (2009) 2–13. [PubMed: 19127562]

[35]. Sade J, Mucociliary flow in the middle ear. Ann Otol Rhinol Laryngol. 80(3) (1971) 336–41. [PubMed: 5578781]

[36]. Salt AN, Hartsock J, Plontke S, LeBel C, Piu F, Distribution of dexamethasone and preservation of inner ear function following intratympanic delivery of a gel-based formulation. Audiol Neurootol. 16(5) (2011) 323–35. [PubMed: 21178339]

[37]. Rutt AL, Hawkshaw MJ, Sataloff RT, Incidence of tympanic membrane perforation after intratympanic steroid treatment through myringotomy tubes. Ear Nose Throat J. 90(4) (2011) E21.

[38]. Rarey KE, Luttge WG, Presence of type I and type II/IB receptors for adrenocorticosteroid hormones in the inner ear. Hearing Research. 41 (1989) 217–21. [PubMed: 2530200]

[39]. Nagura M, Iwasaki S, Wu R, Mizuta K, Umemura K, Hoshino T, Effects of corticosteroid, contrast medium and ATP on focal microcirculatory disorders of the cochlea. Eur J Pharmacol. 366(1) (1999) 47–53. [PubMed: 10064151]

[40]. Vivero RJ, Joseph DE, Angeli S, He J, Chen S, Eshraghi AA, Balkany TJ, Van de Water TR, Dexamethasone base conserves hearing from electrode trauma-induced hearing loss. Laryngoscope. 118(11) (2008) 2028–35. [PubMed: 18818553]

[41]. Hahn H, Salt AN, Biegner T, Kammerer B, Delabar U, Hartsock JJ, Plontke SK, Dexamethasone levels and base-to-apex concentration gradients in the scala tympani perilymph after intracochlear delivery in the guinea pig. Otol Neurotol. 33(4) (2012) 660–5. [PubMed: 22588238]

[42]. Zhao D, Tong B, Wang Q, Hellstrom S, Duan M, A comparison of effects of systemic and intratympanic steroid therapies for sudden sensorineural hearing loss: A meta-analysis. J Otol. 11(1) (2016) 18–23. [PubMed: 29937806]

[43]. Herr I, Ucur E, Herzer K, Okouoyo S, Ridder R, Krammer PH, von Knebel Doeberitz M, Debatin KM, Glucocorticoid cotreatment induces apoptosis resistance toward cancer therapy in carcinomas. Cancer Res. 63 (2003) 3112–20. [PubMed: 12810637]

[44]. Coukell AJ, Balfour JA, Levonorgestrel subdermal implants. A review of contraceptive efficacy and acceptability. Drugs. 55(6) (1998) 861–87. [PubMed: 9617600]

[45]. Smith TJ, Pearson PA, Blandford DL, Brown JD, Goins KA, Hollins JL, Schmeisser ET, Glavinos P, Baldwin LB, Ashton P, Intravitreal sustained-release ganciclovir. Arch Ophthalmol. 110(2) (1992) 255–8. [PubMed: 1310588]

[46]. Driot JY, Novack GD, Rittenhouse KD, Milazzo C, Pearson PA, Ocular pharmacokinetics of fluocinolone acetonide after Retisert intravitreal implantation in rabbits over a 1-year period. J Ocul Pharmacol Ther. 20(3) (2004) 269–75. [PubMed: 15279731]

[47]. Jaffe GJ, McCallum RM, Branchaud B, Skalak C, Butuner Z, Ashton P, Long-term follow-up results of a pilot trial of a fluocinolone acetonide implant to treat posterior uveitis. Ophthalmology. 112(7) (2005) 1192–8. [PubMed: 15921758]

[48]. Baker MI, Walsh SP, Schwartz Z, Boyan BD, A review of polyvinyl alcohol and its uses in cartilage and orthopedic applications. J Biomed Mater Res B Appl Biomater. 100(5) (2012) 1451–7. [PubMed: 22514196]

[49]. DeMerlis CC, Schoneker DR, Review of the oral toxicity of polyvinyl alcohol (PVA). Food Chem Toxicol. 41(3) (2003) 319–26. [PubMed: 12504164]

[50]. Chattopadhyay H, De AK, Datta S, Novel Starch-PVA Polymer for Microparticle Preparation and Optimization Using Factorial Design Study. Int Sch Res Notices. (2015) 261476. doi: 10.1155/2015/261476. [PubMed: 27347511]

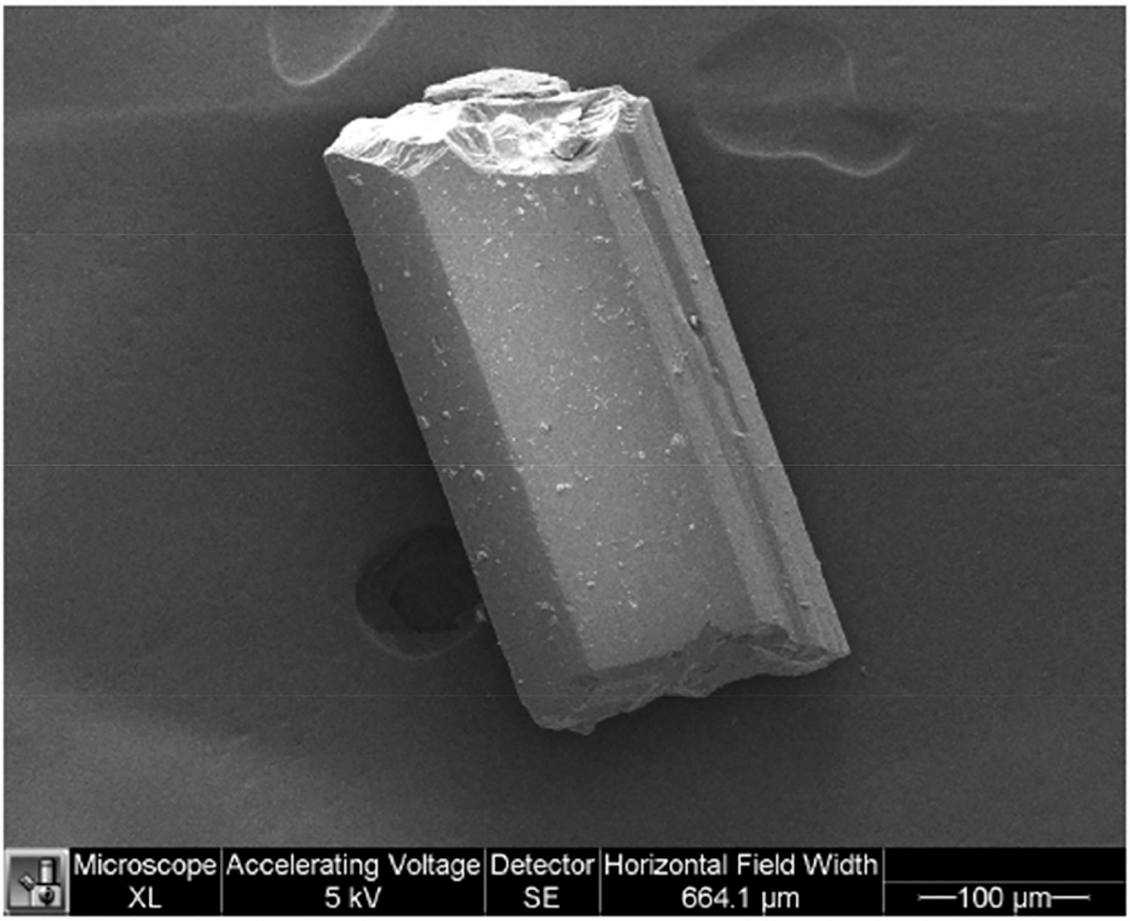
[51]. Chiang CS, Tseng YH, Liao BJ, Chen SY, Magnetically Targeted Nanocapsules for PAA-Cisplatin-Conjugated Cores in PVA/SPIO Shells via Surfactant-Free Emulsion for Reduced Nephrotoxicity and Enhanced Lung Cancer Therapy. Adv Healthc Mater. 4(7) (2015) 1066–75. [PubMed: 25656800]

[52]. Oun R, Plumb JA, Wheate NJ, A cisplatin slow-release hydrogel drug delivery system based on a formulation of the macrocycle cucurbit[7]uril, gelatin, and polyvinyl alcohol. J Inorg Biochem. 134 (2014) 100–5. [PubMed: 24595010]

[53]. Azhar FF, Shahbazpour E, Olad A, pH sensitive and controlled release system based on cellulose nanofibers-poly vinyl alcohol hydrogels for cisplatin delivery. Fiber Polym. 18(3) (2017) 416–23.

[54]. Koçyiğit A, Dicle O, Göktay Y, Astarcıoğlu I, The effect of using different embolic agents on survival in transarterial chemoembolization of hepatocellular carcinoma: gelfoam versus polyvinyl alcohol. Diagn Interv Radiol. 20 (2014) 323–29. [PubMed: 24808440]

[55]. Jayasuriya AC, Darr AJ, Controlled release of cisplatin and cancer cell apoptosis with cisplatin encapsulated poly(lactic-co-glycolic acid) nanoparticles. J Biomedical Science and Engineering. 6 (2013) 586–92.



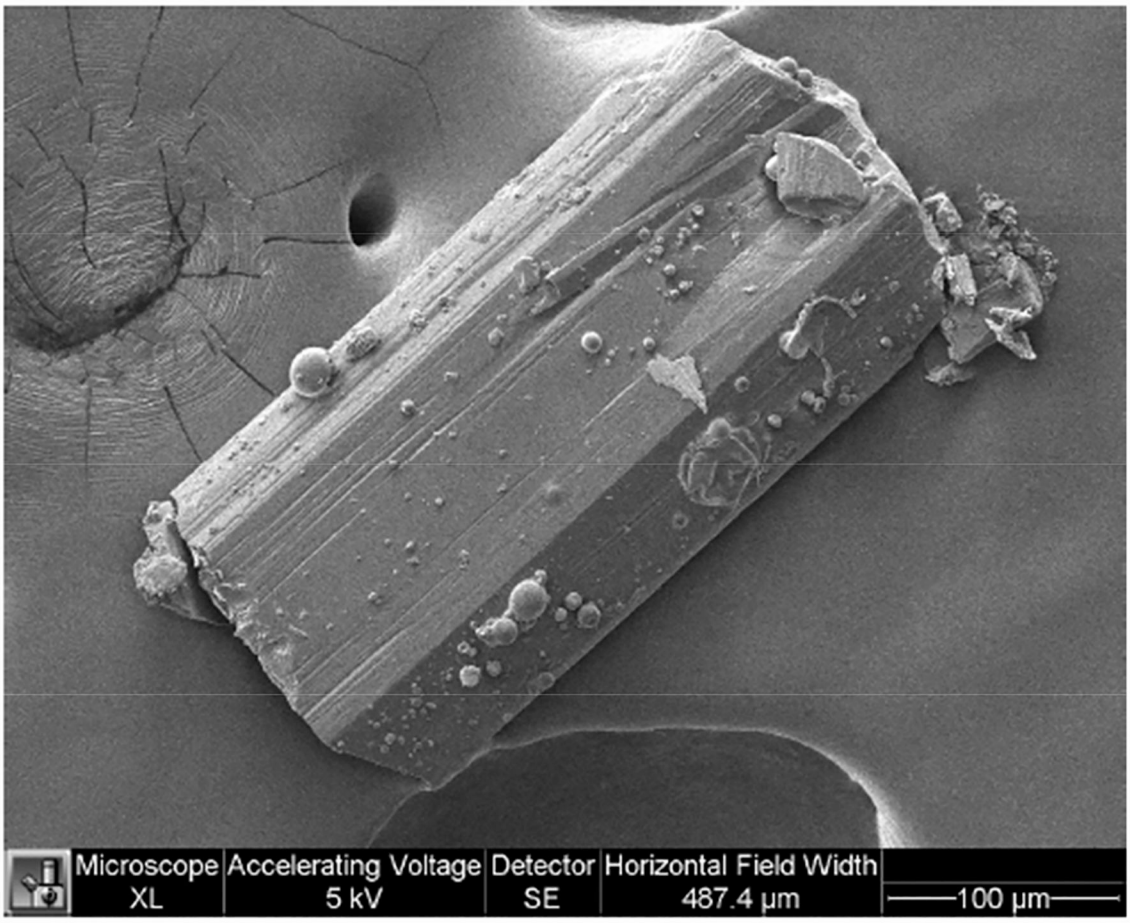


Figure 1: Scanning electron microscopy (SEM) of uncoated and coated (OR-102) fluticasone propionate crystals.

a: SEM image of uncoated crystal. Particle was examined by SEM using an XL 30 S FEG operating at 5kVa (FEI Inc, Hillsboro, OR).

b: SEM image of OR-102. Coated particle was examined by SEM using an XL 30 S FEG operating at 5kVa (FEI Inc, Hillsboro, OR). Moderate agglomeration of the PVA polymer is evident on the surface of the crystal.

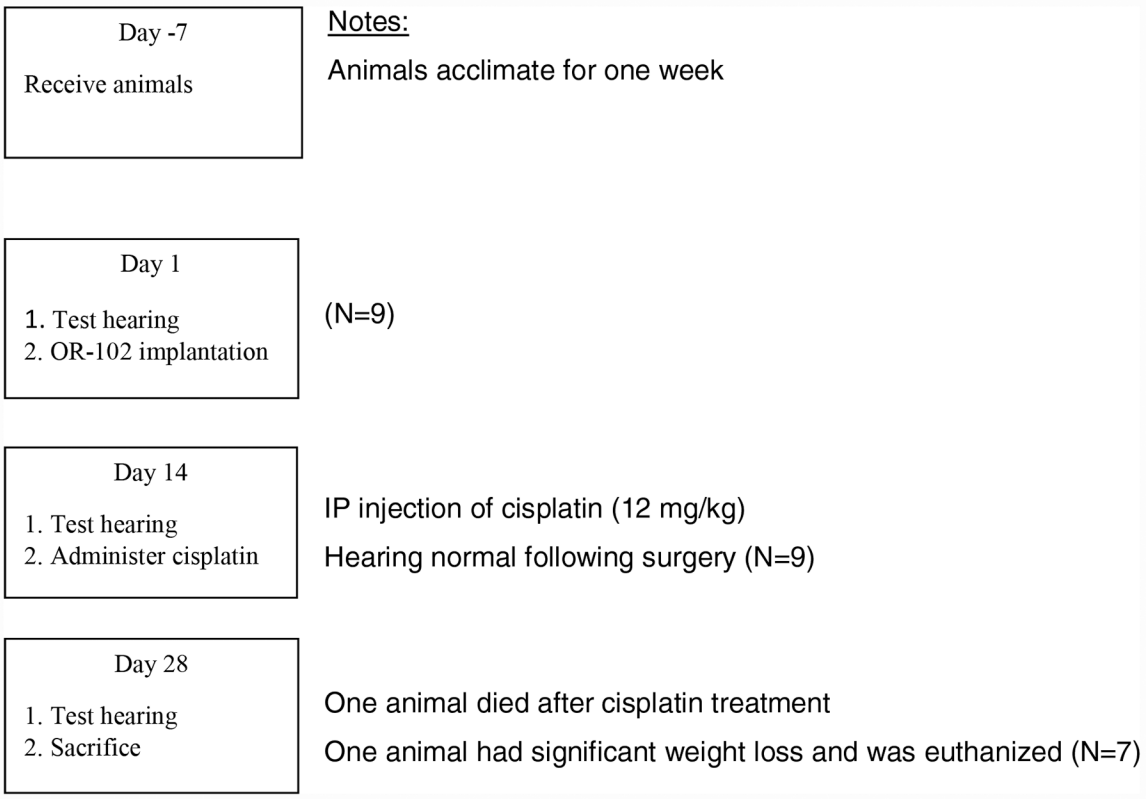
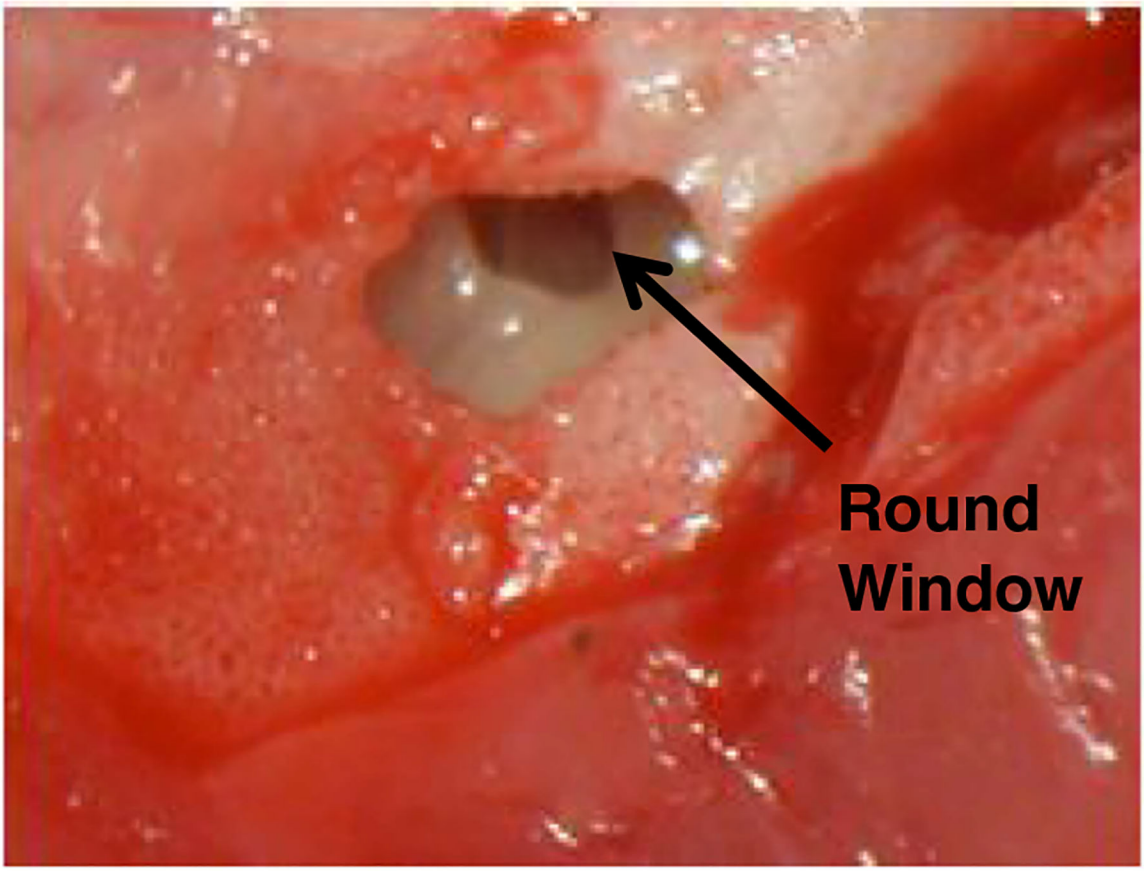
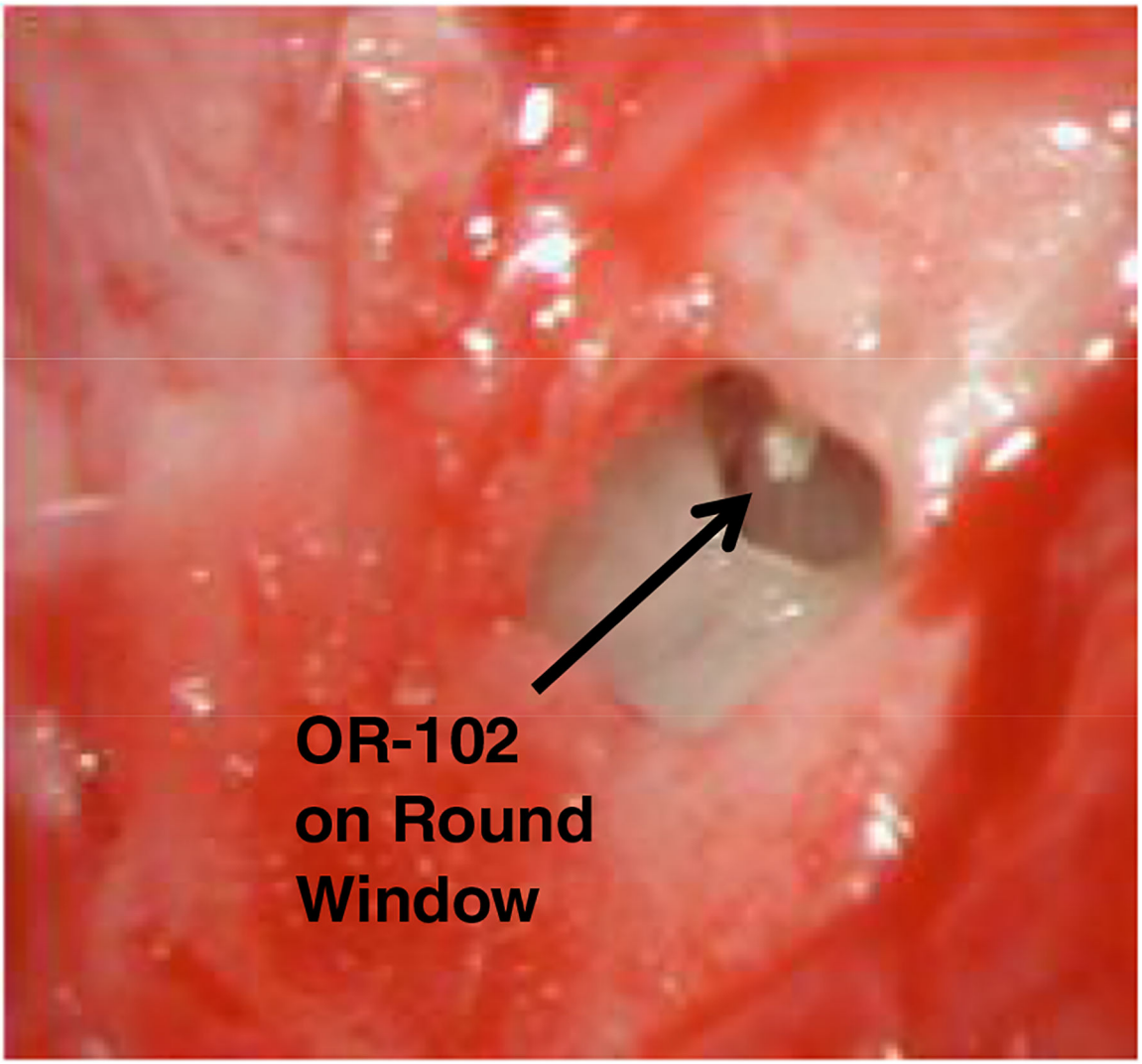


Figure 2.

Study design: Animals were allowed to acclimate for a week prior to OR-102 implantation. At 14 days after implantation cisplatin was administered via intraperitoneal (IP) injection. Hearing was assessed a final time 14 days following cisplatin administration and immediately before euthanasia. One animal died shortly after cisplatin administration. Another animal experienced extreme weight loss after cisplatin administration and was euthanized.





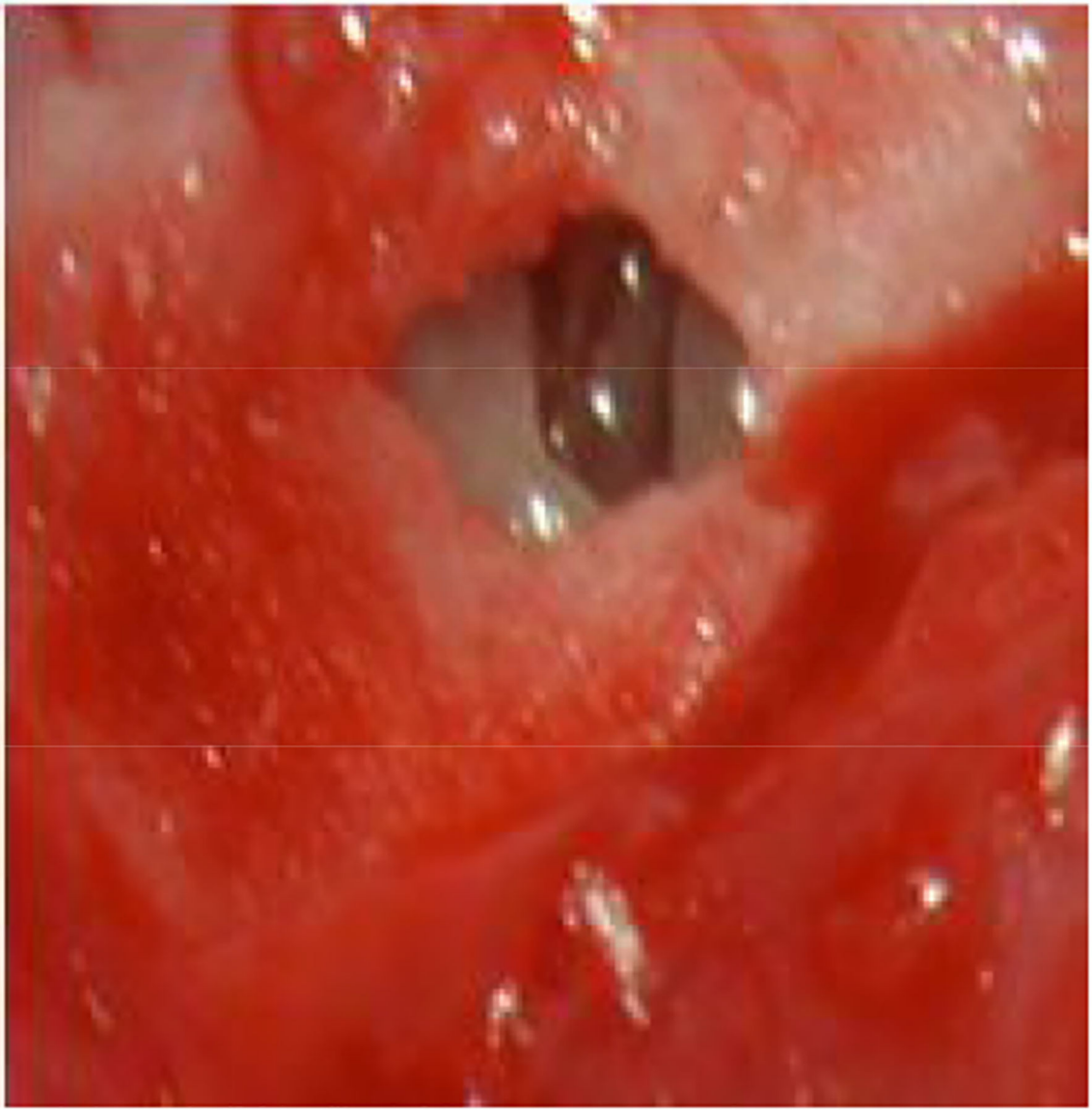


Figure 3: Surgical procedure

a: Round window in the horizontal plane in the experimental ear. This was achieved by drilling a small hole through the bulla using a posterior approach.

b: OR-102 implant sitting on round window. A 32-gauge needle was used to puncture the round window and the OR-102 implant was placed in the scala tympani.

c: Round window after insertion of OR-102. After placement of OR-102 into the round window of the experimental ear, a drop of sodium hyaluronate was placed over the round window injection site to avoid leakage of perilymphatic fluids.

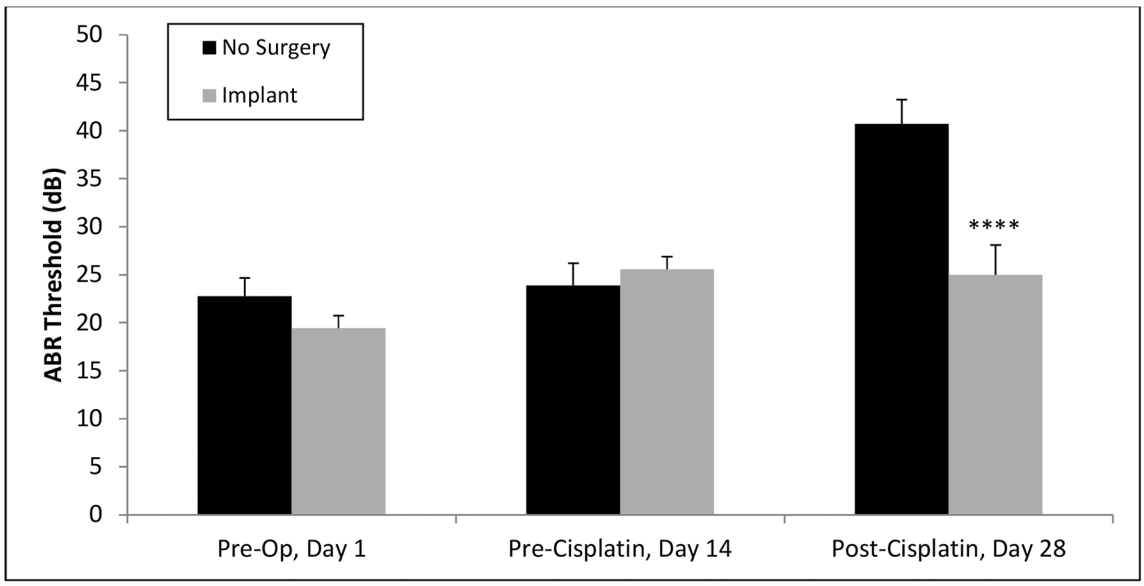


Figure 4.

Auditory brainstem response (ABR) thresholds. Data shows no statistically significant hearing loss between control ears and implanted ears at day 14 based on corresponding ABR thresholds. No surgery (C) and Implant (I) ABR values (Mean±SEM) are as follows: Pre-Op: 22.8±1.9 (C), 19.4±1.3(I); 14 day: 23.9±2.3 (C), 25.6±1.3 (I); 28 day: 40.7±2.5 (C), 25.0±3.1 (I). Statistically significant hearing loss was seen in Control ears (No Surgery) following cisplatin treatment between day 14 and day 28: 23.9±2.3 dB vs. 40.7±2.5 dB; $P \leq 0.0001$, demonstrating cisplatin dependent hearing loss. There was no statistically significant difference in ABR threshold between surgery ears (Implant) between day 14 and day 28: 25.6±1.3 dB vs. 25.0±3.1 dB, $P \geq 0.85$, demonstrating otoprotection from OR-102. Stars indicate statistical significance.

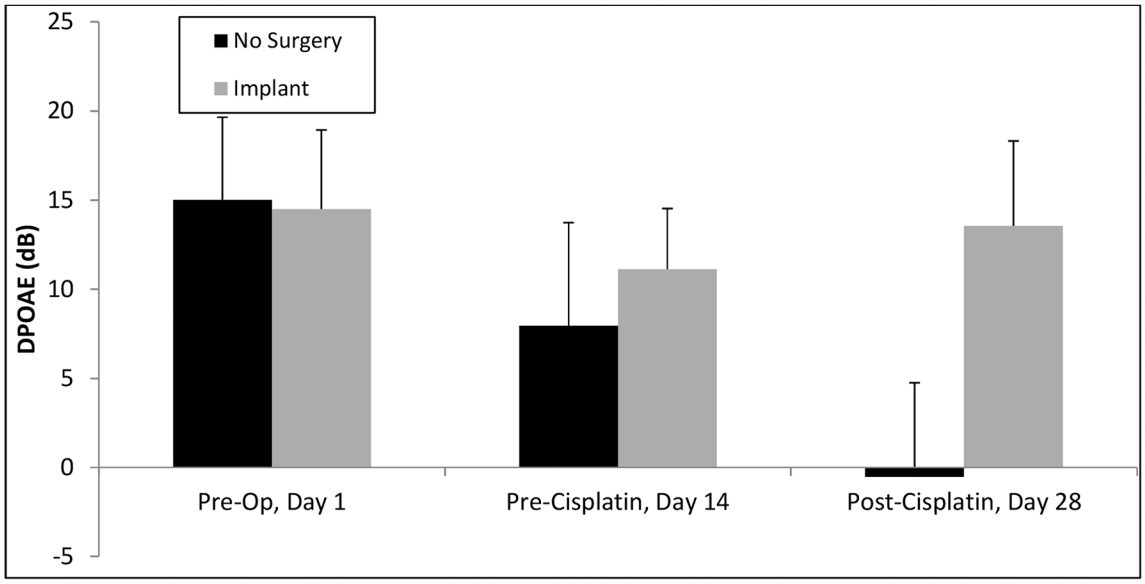


Figure 5:

Distortion product otoacoustic emissions (DPOAEs). No Surgery (C) and Implant (I) DPOAE values (Mean±SEM) are as follows: Pre-Op: 15.0±4.6 (C), 14.5±4.5 (I); 14 day: 7.9±5.8 (C), 11.1±3.4 (I); 28 day: −0.5±5.3 (C), 13.6±4.8 (I). Data demonstrates prevention of cisplatin dependent hearing loss from OR-102 Implant ears 14 days after cisplatin administration (Day 28). DPOAE responses were absent in Control ears 14 days after cisplatin administration but near normal in Implant ears.