

Cisplatin: hearing loss and its prevention

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Abstract

Cisplatin is a well-known treatment of many cancers, yet it puts patients at high risk of hearing loss to further affect their quality of life. In this review, 13 English articles from 2002 to 2014 and one book were reviewed to provide an overview of cisplatin associated ototoxicity: molecular and cellular mechanisms, incidence rates regarding the risk factors and protection.

Introduction

Cisplatin is a chemotherapeutic alkylating agent which is widely known for its effectiveness as a treatment of many malignant tumors such as head and neck, lung, bladder, cervical, ovarian, testicular cancers. Although cisplatin has been synthesized since 1845 as it was synthesized for the first time by Peyrone Owing and it was known as Peyrone's salt, cisplatin entered clinical use only in late 1960 as a therapy for cancers. One of its major side effects is that cisplatin may cause hearing loss with the average incidence of 62%. This hearing loss can be unilateral or bilateral. Also, it can be permanent (irreversible) or transient (can be recovered); it is most often irreversible hearing loss, and it is more serious in pediatric and elderly patients. Both high frequency hearing as well as low frequency hearing may be affected [4].

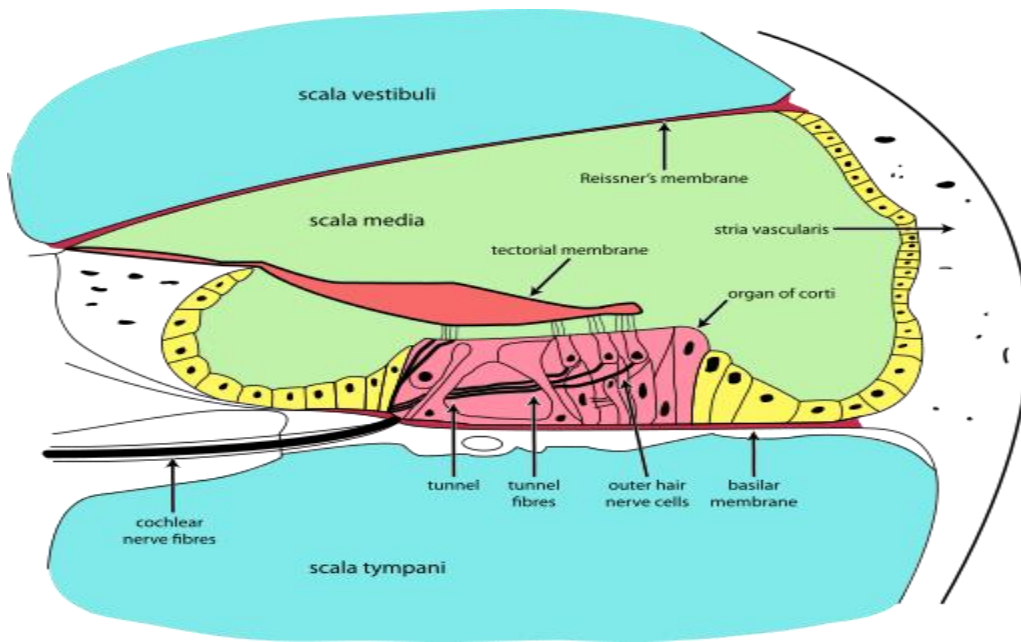
Why cisplatin causes hearing loss

The ear consists of three parts: the outer ear, the middle ear and the inner ear. Sounds move from the outer ear through the middle ear and finally to the inner ear [1].



Ear parts: taking from [1]

The inner ear has the required sensory organs for hearing and balance. One part of the inner ear is the cochlea which is the hearing part in the inner ear. Another part is the semicircular canals which is responsible for balance. Cisplatin damages both the cochlea as well as the semicircular canals, so balance and hearing are both affected. In the inner ear sound waves move through the cochlea that holds the hair cells which are the sensory receptors of the auditory system; signals from hair cells are converted to nerve impulses then sending to the brain [1]. The most susceptible parts of the inner ear to damage by cisplatin are the outer hair cells. This damage occurs gradually from the cochlea's base to the cochlea's apex. Because of this pattern, the hearing loss in the first includes sounds with high frequencies, then it will include low frequencies. With increasing doses or duration of the drug, the damage will include inner hair cells which are more immune, so they will disappear only after the outer hair cells have disappeared completely [12].



Cochlea parts: taking from Wikipedia

The damage of cisplatin also includes spiral ganglion [12] which is a group of nerve cells that send a representation of sound from the cochlea to the brain, so spiral ganglion is the site of stimulation by a cochlear implant [7]. There is a case of a patient who can no longer benefit from his cochlear implant after treatment with cisplatin, although he did not have any problems with the device before the treatment; this case proves a direct damage of cisplatin in the spiral ganglion [12].

The damage of cisplatin in the inner ear occurs through:

Cisplatin accumulation

Following the injection of cisplatin around 25% of the cisplatin is eliminated from the body during the first 24 hours after the administration. Ninety percent of this elimination is occurred through the renal clearance. Cisplatin is collected preferentially by liver, kidney, intestine and minimally by the nervous system.

The damage of the inner ear occurs because of the accumulation of palatinated DNA in the inner ear tissues [4].

Reactive oxygen species (ROS)

As a signaling messengers or natural metabolic byproducts, Reactive Oxygen Species present in all cell types in low concentration. The ROS harmful oxidative action in cells is regulated by some protective mechanisms like antioxidant molecules. The overproduction of ROS would exhaust the antioxidants. The end result of this redox imbalance will be the cell death [5]

Cisplatin generates ROS within the cochlea; superoxide anion and 4-hydroxynonenal anion have been detected in the cochlea after treatment by cisplatin. The way that cisplatin generates ROS is undefined yet, but it is clear that NADPH oxidase isoform NOX3 plays an important role in hearing loss by catalyzing the generation of superoxide in the cochlea [6].

Incidence of hearing loss with risk factors:

Hearing loss related to cisplatin varies from one patient to another. It may be affected by:

Genetic factors

The different incidences of hearing loss in patients who receive similar cumulative cisplatin doses and application schedules prove that there are significant interindividual variations. The possible explanation for this is that specific genes polymorphisms seem to play a role in whether cisplatin would cause hearing loss or not. Data from animal models show that glutathione S-transferases (GSTs) possibly protects against ototoxicity [12].

Data from animal models shows that glutathione S-transferases (GSTs) may protect against ototoxicity. Glutathione S- transferases (GSTs) are a complex of isoenzymes that play an important role in detoxification by catalyzing the conjugation of cisplatin to Glutathione in the purpose of detoxification. Glutathione S- transferases present in the mammalian cochlea; their activity and level of glutathione will decrease when cisplatin-induced ototoxicity develops [2].

The genetic polymorphisms of GSTs: GSTM1, GSTP1 and GSTT1 thought to be responsible for how the individual will respond to the cisplatin ototoxicity. In a study of 173 cancer survivors, the protection from hearing loss induced by cisplatin was referred to the homozygous GSTP1 GG; only two patients out of 28 with this homozygous suffered from severe hearing loss. In the same group, patients with GSTP1 AA or GSTP1 AG were in a higher risk of hearing impairment; GSTP1 AA or GSTP1 AG was noticed in 145 patients of whom 34 patients suffered from severe hearing loss. The protective property of GSTP1 GG was because it has higher substrate specificity for cisplatin. Interestingly, when GSTM1 is present, it can be used as an evidence of cisplatin ototoxicity [12]. The possible explanation for this is that there is a competition for glutathione as substrate of both GSTP1 and GSTM1. GSTM1 likes to use glutathione for reactions rather than detoxification; there will be a limited amount of available substrates for GSTP1, so this will affect the efficiency of GSTP1 [2].

CRT and age

In the a study conducted by Warriar et al., the serial audiograms of 33 children (1-16 years old who are infected with different types of tumors) were obtained before the exposure to cisplatin, and after three to four weeks of the last dose. All children who were included should not have any history of a previous exposure to any kind of toxic drug. Two types of the audiology tests were used to evaluate the auditory function. The first one was the pure tone threshold audiometry. The second one was for younger children who could not respond to the pure tone test which was soundfield behavioral testing. The results for frequencies between 2000-8000 HZ were only analyzed. A hearing threshold of equal to or greater than 30 decibel was used as a clue of a hearing difficulty. Children with brain tumors were around 14/33 (42%). For the whole group, 27 children out of the 33 suffered from hearing loss; 24 suffered from a bilateral hearing loss, and 3 suffered from a unilateral hearing loss. The hearing loss was first detected at 8000 HZ. For the 6 children who their hearing was not affected, there was only one had a brain tumor. In general, the median cumulative dose of cisplatin was higher in children who had hearing loss (400 mg/m²) than in children with unaffected hearing (360 mg/m²).

For the first time hearing loss was detected, the doses of cisplatin were lower in brain patients than other types of tumor patients. For the brain tumor patients, they all received chemo radiation therapy; 13 out of 14 brain tumor patients (92%) had hearing loss, and only one patient did not have hearing loss. For the 19 non brain tumor patients, they all were not exposed to chemo radiation thereby; 14 out of 19 non brain patients (72%) had hearing loss, and the hearing was not impaired in 5 patients.

	N	CDDP, mg/m² (median cumulative dose)
All patients	27	200
Brain tumor	13	180*
Non-brain tumor	14	330
Prechemotherapy CRT	6	240
Postchemotherapy CRT	7	180
CRT	13	180*
No CRT	14	380

* In the comparison of brain tumor vs non-brain tumor and CRT vs no-CRT: $P=0.008$, significant by Mann-Whitney U test. CDDP, cisplatin; CRT, cranial radiotherapy.

The median cumulative doses of cisplatin at first time hearing loss detected: taking from [13]

In this study the patients received CRT are 14.4 times more likely to develop hearing loss in comparison to the patients who did not receive CRT. Also, they found a relation between the age and hearing loss; the children under five years old had a higher incidence of hearing loss; this probably result because of their less mature cochlear and vascular systems which make them more affected by cisplatin ototoxicity [13].

High doses of cisplatin and gender

Another study suggested that the doses of cisplatin per cycle and the cumulative doses are the major factors in developing hearing loss. In case of combination with radiotherapy, low doses of cisplatin (less than 40mg/m²) can decrease the risk of hearing loss than high doses of cisplatin (around 100 mg/m² every 3 weeks) from 78 to 31 percent. Also,

the Cumulative doses of cisplatin of greater than 400 mg/m² or the fractional cisplatin doses of greater than 150 mg/m² were reported as factors that increase the possibility of getting hearing loss. Another factor that could increase the incidences of hearing loss was the gender. For example, the rates of hearing loss were 29.4% in males and 15.5% in females. The hearing loss was transient in 41% of the patients. While, the hearing loss deteriorated in 25% of the patients with persistent hearing loss in the next 2 years [14].

How to protect patients from hearing loss

Many studies on the chemoprotective agents have been done as they possibly could reduce cisplatin related nephrotoxicity, neurotoxicity, and ototoxicity. The majority of these agents are electrophilic thiols that may provide a protection by some ways: binding and inactivation of platinum agents, decreasing DNA damage or scavenging platinum-induced free radicals [8].

Sodium Thiosulfate (STS)

Sodium thiosulfate is a reactive thiol agent that can be used as an antidote to cyanide or nitroprusside poisoning. Sodium thiosulfate can protect cells from being damaged by cisplatin because of the high affinity of sulfur for the platinum group; STS binds to the electrophilic platinum compound inactivating it. It is a nephroprotective and an otoprotective agent with platinum based chemotherapy. In a guinea pig model, STS was an otoprotective agent when it is given two hours after cisplatin. In rats, receiving STS 4 hours after cisplatin can provide a protection from getting hearing loss. In contrast, rats who received STS 8 hours after cisplatin had less protection, and rats who received STS 12 hours after cisplatin had no protection against hearing loss. In another study, the effect of STS on the efficiency of cisplatin was examined in mice. The result was that there is no difference in the efficiency of cisplatin as an anti-cancer agent between the first group of mice which treated by cisplatin only and the other group which exposed to STS after 6 hours of cisplatin. Also, STS can be given as ear drops over the whole period of cisplatin treatment [10].

Antioxidants

Antioxidants are given 6 hours after cisplatin administration but there is a possibility that antioxidants may inactivate cisplatin if antioxidants and cisplatin are both given intravenously because they catalyze the disappearance of platinum. However, giving antioxidants by an alternative route such as transtympanic injection (ex: ear drops) can lead to better results [8].

Aspirin

A new UK trial (COAST) (May-8-2014) investigates if high doses of aspirin can prevent the hearing loss induced by cisplatin. They do a trial on about 88 patients who received cisplatin to treat their cancers. Around half of the patients were given a high dose aspirin of around 4 doses daily for 3 days; one day before the administration of cisplatin and 2 days after. Another 44 patients were treated by placebo for the same days. All patients had a hearing test before getting their treatments and one week, then 3 months after. The main function of aspirin in preventing cisplatin induced hearing loss is that it can prevent the accumulation of free radicals in inner hair cells by mopping them up. The main problem with cisplatin is that it can cause an internal bleeding, so it is important to only give the patient coated aspirin tablets that would be only released when they reach the small intestine. Also, it is important to give the patients drugs that prevent the production of the digestive juices to avoid a stomach bleeding. If this trial succeed aspirin can be used as a part of cisplatin treatment [3].

Vitamin A, C and E

Vitamins A, C and E are antioxidants that can repair the damaged cells, but it is of course not a good idea to use them in a large amount during the treatment by cisplatin. One object of chemotherapy is to kill cancer cells by a process called apoptosis. Antioxidants, however, appear to reduce this process [9].

Conclusion

The ideal protective agent must have three characteristics: first, it should not be toxic because it is not logical to protect from cisplatin damage and cause another damage. Second, it should accumulate in a high concentration in the inner ear organs to achieve a best protection against cisplatin. Finally, the efficiency of cisplatin should not be effected; the cure from cancer is the most important thing. Unfortunately, there is no ideal protective agents have been discovered yet; the need to find an ideal protective agent is really demand to protect the quality of life of many patients [8].

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