REVIEW ARTICLE

Cochleotoxicity monitoring protocol

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Abstract
Introduction: Cochlear damage is frequent in long-term aminoglycosides therapy or chemotherapeutic treatments with platinum-based agents. Despite its prevalence, it is currently underestimated and underdiagnosed. A monitoring protocol is vital to the early detection of cochleotoxicity and its implementation is widely encouraged in every hospital unit. Our aim was to elaborate a cochleotoxicity monitoring protocol for patients treated with platinum compounds or aminoglycosides antibiotics.

Methods: PubMed® database was searched using terms relevant to drug cochleotoxicity in order to identify the most adequate protocol. Several articles and guidelines influenced our decision.

Results: There is no consensus on a universal monitoring protocol. Its formulation and application rely heavily on available resources and personnel. High-frequency audiometry and otoacoustic emissions play an important role on early detection of cochleotoxicity caused by aminoglycoside antibiotics and platinum compounds.

Conclusion: A cochleotoxicity monitoring protocol consisting on an initial evaluation, treatment follow-up and post-treatment evaluation is proposed.

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Keywords
Aminoglycosides; Platinum compounds; Hearing loss; Audiometry, pure-tone; Otoacoustic emissions

PALABRAS CLAVE
Aminoglucósidos; Compuestos de platino; Pérdida de la audición;

Protocolo de monitorización de cocleotoxicidad

Resumen
Introducción: El daño coclear es frecuente en la terapia de aminoglucósidos a largo plazo, o en tratamientos quimioterapéuticos con agentes a base de platino. A pesar de su prevalencia, actualmente está subestimado y subdiagnosticado. Un protocolo de monitorización es vital para la detección temprana de la ototoxicidad, por lo que se incita a su implementación.

* We propose a monitoring protocol for chemically-induced hearing loss.
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Audiometría, tono puro; Emisiones otoacústicas.

en todas las unidades hospitalarias. Nuestro objetivo fue elaborar un protocolo de monitorización de la cocleotoxicidad para pacientes tratados con compuestos de platino o antibióticos aminoglucósidos.

**Métodos:** Se realizaron búsquedas en la base de datos PubMed® utilizando términos relevantes para la cocleotoxicidad de los fármacos con el fin de identificar el protocolo más adecuado. Varios artículos y directrices influyeron en nuestra decisión.

**Resultados:** No hay consenso sobre un protocolo de monitoreo universal. Su formulación y aplicación dependen en gran medida de los recursos y el personal disponibles. La audiometría de alta frecuencia y las emisiones otoacústicas desempeñan un papel importante en la detección temprana de la cocleotoxicidad causada por los antibióticos aminoglucósidos y los compuestos de platino.

**Conclusión:** Se propone un protocolo de monitorización de la cocleotoxicidad, consistente en una evaluación inicial, seguimiento del tratamiento y evaluación postratamiento.

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**Introduction**

According to the American Academy of Otolaryngology Position Statement (American Academy of Otolaryngology–Head and Neck Surgery, revised in 26/09/2015), ototoxicity may be defined as inner ear damage as a consequence of drug or chemical administration. Despite being a concept known for centuries, it was first scientifically described in 1945 by Hinshaw and Feldman on their work with streptomycin.\(^1\)

Since then, more than 200 medications were labelled as potential ototoxic.\(^2\) Aminoglycosides antibiotics (AG) and platinum based chemotherapeutic agents are the most studied ones since they cause cochlear damage in a frequent and permanent manner.\(^3\)

Since its discovery in 1940s by Waksman and his team, streptomycin and the more recent aminoglycosides have been widely used for several gram negative bacteria and Mycobacterium tuberculosis infections.\(^4\)\(^5\) They inhibit protein synthesis by binding to the bacterial 30S ribosomal subunit\(^4\)\(^5\) and are largely used mainly due to low price, broad-spectrum efficacy, low incidence of allergic reactions and wide accessibility.\(^6\) Due to these reasons, in the developing countries, ototoxicity due to aminoglycosides antibiotics is a major public health issue.\(^7\)

Despite being known since the 19th century as Peyronie’s salt, cisplatin (CP) antineoplastic action was only discovered in the following century by Rosenberg and his team.\(^2\) Since then cisplatin have been used to treat several malignancies such as head and neck primary and metastatic cancer.\(^2\)\(^4\) Cancer cell uptakes cisplatin that binds covalently to DNA, further initiating down-stream apoptotic pathways.\(^5\)\(^6\) Carboplatin and oxaplatin, although less ototoxic than cisplatin, seem to be less effective than cisplatin against some cancers.\(^2\)

The molecular pathways of ototoxicity are complex and incompletely understood; several necrotic and apoptotic pathways may be involved\(^8\) but its description is beyond the scope of this article. The common feature of AG and CP ototoxicity is the production of Reactive Oxidative Species (ROS) and their effects on hair cell death.\(^5\)\(^6\)\(^8\)\(^9\) Besides that, there is a tonotopic pattern of cochlear hair cell loss present both in AG and CP ototoxicity – it affects initially the outer hair cells of basal part of the cochlea (high frequencies) further progressing not only from base-to-apex (lower frequencies) but also from outer-to-inner cells.\(^2\)\(^4\)\(^5\)\(^8\)\(^9\)

The increased susceptibility of basal hair cells may be due to less effective calcium-handling mechanisms and consequently calcium overload, like in noise-induced hearing loss. In fact, the relative lack of ototelin on basal outer cells, a calcium sensing protein involved in hair cell survival, support this theory.\(^8\) Alternatively, basal outer cell vulnerability may be explained by the higher presence of transient receptor potential vanilloid 1 and 4 (the cell entry route of aminoglycosides) or by lower expression of the anti-oxidant glutathione.\(^5\)

Cochleotoxicity seems to be underestimated due to audiometric testing and pharmacologic variability (no relation among toxicity and drug dosage, plasma level or crossed renal toxicity).\(^1\)\(^10\) Its prevalence is probably underestimated considering the absence of clinical signs in early ototoxicity due to the tonotopic pattern described elsewhere.\(^1\)\(^12\) The reported prevalence varies widely due to the reason explained above: AG ototoxicity may range from 0 to 63%, although in long-term treatments (6m–1yr) virtually all patients are affected; CP ototoxicity reports range from 3% to 100%.\(^1\)\(^3\)\(^12\)

Several risk factors for AG and CP ototoxicity were identified: poor diet and low nutritional state (anaemia and hypoalbuminemia), kidney failure, previous hearing loss, acoustic trauma and HIV infection. Simultaneous treatment with loop diuretics (furosemide, ethacrynic acid) or anti-neoplastic drugs (vincristine, ifosfamide) may potentiate AG or CP toxicity, respectively. Young and old age as well as genetic polymorphisms (mutation in the 12S ribosomal RNA for AG and glutathione s-transferase polymorphisms for CP) may also be implied. Therapeutic details such as quick intravenous bolus and coexistent cranial radiotherapy also play a role in CP ototoxicity potentiation.\(^2\)\(^5\)\(^7\)\(^13\)
Cochleotoxicity monitoring protocol

There is still no universally accepted monitoring protocol for cochleotoxicity.\textsuperscript{6,10} Our aim was to review the available literature and elaborate a monitoring protocol adapted to Portuguese reality and to the resources available on our centre.

Materials and methods

Articles relative to ototoxicity monitoring were searched in PubMed\textsuperscript{®} database. Mesh terms “hearing loss”, “aminoglycosides” and “cisplatin” were used. Articles in English or Portuguese published in the last ten years were included (17). 3 articles fit the aim of this work; quoted articles considered relevant for the issue were also included, as well as position statement from worldwide societies and, when available, guidelines on ototoxicity monitoring.

Results and discussion

A monitoring protocol for ototoxicity aims to detect hearing loss as early as possible.\textsuperscript{3,4} Since vestibular toxicity monitoring remains arbitrary,\textsuperscript{4} only cochleotoxicity is approached in this work. Some medications are more prone to cause hearing loss what makes patients taking those drugs obvious candidates for monitoring.\textsuperscript{4,5,10} Among these patients, the ones with comorbidities wich render them more susceptible for ototoxicity (anaemia, kidney failure, HIV infection, old age) and those taking other cochleotoxic medications (loop diuretics, vincristine) deserve special attention.\textsuperscript{2,11} There is consensus in adapting monitoring tests to patients cooperation level.\textsuperscript{3,10}

There are no standard criteria universally used to define cochleotoxicity.\textsuperscript{4,14} ASHA criteria (1994) remain the most widely used, defining a significant hearing loss as: (a) $\geq$20 dB decrease at any tested frequency, (b) $\geq$10 dB decrease at any two adjacent frequencies, or (c) loss of response at three consecutive frequencies where positive responses were previously given.\textsuperscript{3,4}

Initial assessment aims to document baseline hearing and should be as complete as possible, including all the test needed in subsequent evaluations.\textsuperscript{3,11} Ideally performed before any drug administration, when taking AG it may be delayed to 72 h after initial dosage since no cochlear damage has been histologically shown before that; since CP may cause cochlear damage only 24 h after initial dosage, initial evaluation when taking platinum compounds should not be deferred further.\textsuperscript{3,10,11}

Cochleotoxicity monitoring protocol (Table 1)

Baseline evaluation must comprise a detailed medical history focusing on medical comorbidities, medications taken and other risk factors (e.g.: noise or radiation exposure).\textsuperscript{11} Otoscopy and immittance tests (tympanometry and acoustic reflex testing) are vital to assure middle ear and conduction system integrity.\textsuperscript{10,11} Full audiometric evaluation in conventional frequencies – pure-tone air and bone thresholds, speech recognition thresholds and discrimination testing – represents the patients hearing acuity before treatment.\textsuperscript{3,4,10}

<table>
<thead>
<tr>
<th>Patient selection</th>
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<td>Patients receiving platinum compounds for head and neck malignancies</td>
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<td>Patients receiving AG for pulmonary tuberculosis</td>
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Baseline evaluation

AG: <72 h after first dosage
CP: <24 h after first dosage
Cooperative patients: otoscopy, immittance testing, pure-tone and speech audiometry (conventional frequencies), HFA
Non-cooperative patients: otoscopy, DP-OAE

If loss detected:

Immittance testing, speech audiometry (if cooperative), DP-OAE/BERA
Repeat in 24 h
Weekly evaluation till stabilization
Ponder drug withdrawal, dosage modification or treatment completion

Post-treatment evaluation

At treatment completion, 3 and 6 months after
If simultaneous head/neck radiation evaluate also at 12 and 24 months
Cooperative patients: pure-tone audiometry (conventional frequencies), HFA
Non-cooperative patients: DP-OAE

If loss detected:

Immittance testing, speech audiometry (if cooperative), DP-OAE/BERA
Repeat in 24 h
Weekly evaluation till stabilization
Ponder hearing aid

Despite its importance in defining pre-treatment hearing acuity in speech frequencies and speech recognition, conventional frequency audiometry lacks sensitivity in detecting early cochleotoxicity.\textsuperscript{7} As described elsewhere, early cochleotoxic lesion affects the basal cochlea and high-frequency hearing\textsuperscript{1,3,6}; thus, High-Frequency Audiometry (HFA) – 8–20 kHz – is universally accepted as the most sensitive and specific test for detecting early cochleotoxicity.\textsuperscript{6,10,11,15} Despite this, HFA is limited in patients with previous hearing loss (such as most elderly patients suffering from presbyacusis)\textsuperscript{6} and depends on patients response and cooperation.\textsuperscript{10} Besides, HFA still lacks universal criteria for normality\textsuperscript{6}; however, a recent study...
Patients

However, Otoacoustic emissions (OAE) objectively evaluate outer hair cells integrity and detect cochleotoxicity earlier than conventional audiometry. When choosing between transient-evoked and Distortion Products Otoacoustic Emissions (DP-OAE), the last show several advantages: allow evaluation of higher frequencies (above 4 kHz) thus detecting cochleotoxicity earlier, are more sensitive because are present in patients with more severe sensorineural loss, and are more frequency-specific since are elicited using two tones – for this reasons, they tend to be preferred. DP-OAE are particularly useful for non-cooperative patients due to time-efficiency, portability and test–retest reliability. However, commercially available equipment does not allow DP-OAE testing through ultra-higher frequencies (6–12 kHz) and there are still no universally accepted criteria for DP-OAE interpretation.

Treatment monitoring: patients taking AG should be evaluated every 2–3 days but for practical reasons weekly or biweekly assessments seem acceptable. For CP treatments, there is consensus in evaluating patients 24 h before every dosage.

Medical evaluation begins by asking the patient about newly developed symptoms such as hearing impairment, tinnitus or vertigo, and synergistic factors such as noise exposure or other ototoxic drugs. In cooperative patients this is followed by otoscopy, conventional frequency and high frequency pure-tone audiometry. Since most changes in hearing are observed within one octave of the highest audible frequency for each patient, a series of shortened protocol for HFA application have been proposed and shown viable. If hearing loss is suspected further testing is required: immittance measures to exclude middle ear pathology, speech audiometry to guide counselling and rehabilitation process, DP-OAE or Brainstem-Evoked Response Audiometry (BERA) to confirm cochlear damage as the source of hearing loss. The patients are retested in the 24 h to confirm hearing loss and is assessed weekly till stabilization. When ototoxicity is confirmed, treatment modification (drug withdrawal or dosage change) must be pondered; strategies to block ROS production and prevent inner ear damage are being studied and represent a logical step in cochleotoxicity prevention.

In non-cooperative patients behavioural tests are not possible and thus a shortened protocol consisting of otoscopy, immittance tests and DP-OAE is used. Post-treatment evaluation allows detection of late cochleotoxic effects, and since ototoxic drugs were proven to be present in hair cells 11 months after treatment cessation, patients should re-evaluate on treatment completion, 3 and 6 months after. Patients who received head and neck radiation should be monitored in the next year or two. When hearing loss is detected, weekly evaluation till stabilization is advisable.

Considerations regarding special populations: HFA and DP-OAE are of limited use in elderly people suffering from age related hearing loss. In these cases, DP-OAE seem to be more sensitive than HFA. However, since in this patients high frequency hearing is already compromised at treatment institution, monitoring should focus on preserving speech frequencies, which is achieved by conventional frequency audiometry. Paediatric populations represent a particular challenge since they are in a language developing phase, in which hearing impairment may cause serious limitations on speech comprehension and production. Due to behavioural immaturity, cooperation is frequently undermined and objective methods are needed. Hence, DP-OAE represent a valid and reproducible method. BERA are sometimes considered as an alternative to DP-OAE for ototoxic monitoring on young populations. However, the fact that most protocols are limited to 1–4 kHz frequencies and the repetitive need of sedation, makes this test unadvisable as a monitoring method.

Tinnitus and vertigo are potential indirect signs of ototoxic damage and its presence should be asked in every consultation. However, universal guidelines for vestibular toxicity are nonexistent and the discussion about the most adequate tests for vestibular monitoring is beyond the scope of this article.

Conclusion

Cochleotoxicity monitoring aims to detect an early hearing loss and ultimately avoid hearing impairment in speech frequencies. Comprehensive, serial and prospective evaluations of hearing function remain the only option to do so. Protocol implementation is dependent on the target population, human and material resources available and the refer network among health professionals. From our understanding, there are no published cochleotoxicity monitoring protocols designed for Portuguese population and Portuguese health care facilities. Considering the widespread usage of ototoxic medications and the disability level caused by hearing impairment, implementation of an cochleotoxic monitoring protocol should be regarded as a standard practice. This protocol provides a basis to do so.

Funding

None.

Conflicts of interest

None.

References

Cochleotoxicity monitoring protocol


