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REVIEW ARTICLE

Cochleotoxicity monitoring protocol☆

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KEYWORDS
Aminoglycosides;
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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.

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

Protocolo de monitorización de cocleototoxicidad

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 cocleototoxicidad 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 cocleototoxicidad 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 cocleototoxicidad causada por los antibióticos aminoglucósidos y los compuestos de platino.
Conclusión: Se propone un protocolo de monitorización de la cocleototoxicidad, consistente en una evaluación inicial, seguimiento del tratamiento y evaluación postratamiento.

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.[1,2] Since then, more than 200 medications were labelled as potential ototoxic.[3] 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.[2,4] They inhibit protein synthesis by binding to the bacterial 30S ribosomal subunit[5,6] and are largely used mainly due to low price, broad-spectrum efficacy, low incidence of allergic reactions and wide accessibility.[2] Due to this 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 *Peyrone'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 otorfelin 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.[8]

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).[3,10] Its prevalence is probably underestimated considering the absence of clinical signs in early ototoxicity due to the tonotopic pattern described elsewhere.[11,12] 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%.[3,5,12]

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 antineoplastic 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.[2,7,13]