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Drugs inducing hearing loss, tinnitus, dizziness and vertigo: an updated guide

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Abstract. – OBJECTIVE: The awareness of audio-vestibular side effects of drugs, such as hearing loss, tinnitus, dizziness and vertigo, has widely increased in the recent years. The present guide represents an update of the previous documents published by the authors in 2005 and 2011 on drug-induced ototoxicity and vestibulotoxicity.

MATERIALS AND METHODS: The authors performed a comprehensive analysis of audio-vestibular side effects of commercially available drugs based on the British National Formulary, a pharmaceutical reference book that contains a wide range of useful information and advice on prescription and pharmacology.

RESULTS: Commercially available drugs and their active principles have been classified based on their audio-vestibular side effects, as reported by the pharmaceutical companies and/or health agencies. Drugs have been categorized based on the field of application, the therapeutic indication and the pharmacological properties.

CONCLUSIONS: General practitioners, otolaryngology, neurology and audiology specialists should be aware of possible audio-vestibular side effects of drugs, such as hearing loss, tinnitus, dizziness and vertigo. The present guide represents a practical tool to rapidly identify potential audio-vestibular side effects of drugs as reported by the pharmaceutical companies and/or health agencies.

Key Words:
Pharmacovigilance, Side effects, Ototoxicity, Tinnitus, Vertigo.

Abbreviations
NSAIDs: nonsteroidal anti-inflammatory drugs; ADRs: Adverse Drug Reactions; PTA: pure tone audiometry.

Introduction

Ototoxicity is an undesirable effect of some drugs that induce reversible and irreversible damage of the inner ear structures, including the cochlea and the vestibule, causing temporary or permanent hearing loss, tinnitus and/or balance alterations[1-3].

Cochlear damage manifests through sensorineural hearing loss and tinnitus. Tinnitus can be associated to hearing loss or appear in the absence of clinically evident hearing alterations; tinnitus may also be a consequence of central drug-induced alterations[4,5]. Vestibular injury may cause balance disorders, such as instability, difficulty in maintaining straight posture, unsteadiness, loss of balance and dizziness[6,7]. Ototoxic effects depend on duration of therapy, route of administration, infusion rate, dosage, individual sensitivity, genetic predisposition and altered renal and hepatic functions. Although single administrations may have ototoxic effects, long-term therapies have a higher risk of producing ototoxic side effects[1-5,8-10].

Drug Ototoxicity

Ototoxic drugs

Drug classes most associated with ototoxicity include antibiotics, such as aminoglycosides, glycopeptides and macrolides[11-16]; platinum-based antitumor drugs[5,17-20]; loop diuretics, such as furosemide[21,22]; antimalarial drugs, such as quinine and chloroquine[23,24]; nonsteroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid[10,25,26].

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The drug class whose ototoxicity has been most studied are aminoglycosides and, to date, their ototoxic effects are well known[11,13,15]. Some of these antibiotics tend to cause more damage to the cochlear function (Dihydrostreptomycin, Kanamycin, Neomycin, Amikacin), others to the vestibular function (Streptomycin, Gentamicin, Tobramycin, Sisomicin); sometimes, both functions are involved. The risk of ototoxicity increases with the concomitant use of diuretics, in the presence of renal failure, and for long-term treatments[11,13,15].

Macrolides and glycopeptides have limited ototoxicity. Macrolides, such as Erythromycin and Azithromycin are ototoxic only if used at high doses and if administered intravenously[27,28]. Glycopeptides, such as Vancomycin and Teicoplanin are ototoxic in the presence of renal failure[29].

Platinum-derived chemotherapies, such as cisplatin, carboplatin and oxaliplatin have a potent ototoxic action. These drugs can cause bilateral, progressive, non-reversible, dose-dependent sensorineural hearing loss that may occur immediately after the first administration or sometimes even several months after completing treatment. Hearing should be monitored before starting chemotherapy, during and after completing treatment. The risk of hearing loss in patients treated with cisplatin ranges from 10 to 90% for multiple administrations, while it is nearly 30% for a single dose[17-20,30,31].

Other ototoxic drugs include furosemide and other loop diuretics, that may induce temporary or permanent hearing loss if used at high doses and for prolonged periods[21,22]; antimalarial drugs, such as quinine and chloroquine[23]; NSAIDs and acetylsalicylic acid can cause hearing loss and generally reversible and dose-dependent tinnitus, especially in long-term treatment[10,23,25,32,33].

Ototoxic drugs trigger complex biochemical alterations at the endolymphatic level with consequent modification of the endocochlear potential and cochlear damage. Histopathological alterations have been highlighted in central structures (degenerative phenomena of cochlear and vestibular nuclei) and peripheral organs (destruction of sensory cells of maculae, ampullary cupula, Organ of Corti and spiral ganglion). Cochlear lesions, especially when involving the inner hair cells and spiral ganglion fibers, may be present without a clinically evident hearing loss[8,34,35].

Main Audiological Symptoms

Ototoxicity can present with different symptoms: sensorineural hearing loss, tinnitus, aural fullness, dizziness, and vertigo[1-4]. These symptoms may have a simultaneous or independent onset, can develop rapidly or gradually and can be reversible or irreversible. Audiological symptoms following ototoxic drug administration are subject to high interindividual variability due to differences in genetic factors, pharmacokinetics, metabolic status of the individual and co-morbid medical conditions[1,3,5,8,12,18,19,28,36-39].

Sensorineural hearing loss can follow functional impairment and/or cellular degeneration of tissues of the inner ear, mainly outer and inner hair cells. Hearing loss may present in the early stages immediately or within 7-10 days from drug administration as a bilateral symmetric hearing loss with different paths. Initially, hearing loss tends to affect high frequencies followed by medium and low frequencies, although the audiometric aspect may vary and sometimes the frequencies affected by the damage are the middle frequencies, with preservation of the low and high frequencies[2,8,40-42]. Hearing loss following ototoxic treatment may resemble that found in Meniere's Disease (MD), an idiopathic inner ear disorder characterized by recurrent vertigo, fluctuating hearing loss, aural fullness and tinnitus[43-45]. Furthermore, drugs used to treat MD include intratympanic gentamicin, an ablative procedure that has been shown[46,47] to obtain high rates of vertigo control with dose-dependent risk of hearing deterioration and healthy-side vestibular hypofunction; recent studies[48,49] have demonstrated that intratympanic administration of low-dose gentamicin following a titration protocol can produce a satisfactory control of vertigo without causing significant cochlear damage.

Tinnitus following treatment with ototoxic drugs may be continuous or, rarely, pulsatile. Tinnitus is mainly low or high pitched, often associated to hearing loss and matching its frequency[50-52]. Pulsatile tinnitus can also be found in patients with ototoxic damage; although it mainly has a vascular origin and not a direct relation to ototoxicity, it may be indirectly related to drug administration for the effects of these drugs on the vascular flow or systemic blood pressure. In these cases, normal flow sounds within the body are perceived more intensely[53]. Pulsatile tinnitus is usually unilateral, unless the underlying vascular pathology is bilateral, it can have an arterial or venous origin, or it may originate between arteries and veins[53-55].

Vestibular symptoms of vestibulotoxicity can be unilateral and bilateral and include oscillop-

sia, dizziness, motion sickness, and unsteadiness when standing or walking, especially in the dark[14,16,56]. Symptoms can range from mild to disabling, depending on the severity of the vestibular toxicity and on the functional integrity of other sensory systems that contribute to the maintenance of balance and equilibrium[14,16,56].

Clinical diagnosis and management of ototoxicity

Symptoms of ototoxicity may appear during or after the therapy and are usually bilateral, even if sometimes firstly involve one side and then the other. In some cases, the symptoms disappear when treatment is finished; in others, the damage can be irreversible[1-3,5,8,28,37].

The diagnosis of ototoxicity is based on patient's history and audiological evaluation with pure tone audiometry (PTA). In patients receiving long-term therapy with ototoxic drugs, it is recommended to perform PTA every three to six months even after the end of the treatment. In the case of a confirmed reduction in hearing capacity, other exams, such as otoacoustic emissions, vocal audiometry, auditory brainstem responses and vestibular examination should be performed[1-3,5,8,28,37].

Clinical indications may help preventing damages resulting from the use of ototoxic drugs; they include the control of renal and hepatic functions, the use of intravenous route only in selected cases, and the avoidance of long-term treatments. However, given the high inter-individual variability due to endogenous and exogenous factors, it is difficult to predict the individual susceptibility to hearing damage[38,57-62].

To date, available options to reduce the risk of irreversible inner ear damage due to drug ototoxicity rely on the use of alternative therapies without known ototoxic potential or on the simultaneous administration of protective therapies to preserve the inner ear structures, such as high-dose antioxidant treatments that have been shown to be effective in experimental protocols[23,25,32,39,63-74].

Future options to recover hair cell loss following ototoxic treatment include the use of stem cells. Many studies[75-77] have focused on regenerating auditory cells after damage through endogenous stem cell activation and exogenous stem cell transplantation, demonstrating using *in-vitro* and *in-vivo* models that stem cells may be capable of differentiating into hair cells. However, the use of stem cells in hearing restoration is still limited by several problems, such as the successful differentiation of stem cells into functional cells, and require the evaluation of complex factors, such as stem cell-type choice, signaling pathway regulations, transplantation approaches, internal environment of the cochlea, and external stimulation[78-80]. Recent findings[75-77,81] raise hope for the future development of stem-cell-based treatment regimens that could be used to repair damages following treatment with ototoxic drugs.

Guide Presentation

The present guide represents an update of the previous documents published by the authors in 2005 and 2011 on drug-induced ototoxicity and vestibulotoxicity[36,82].

Information to classify the otologic side effects caused by commercially-available drugs have been collected from the British National Formulary[83], a pharmaceutical reference book, pharmaceutical companies and health agencies.

In the present guide, the list of active principles and their respective commercial products has been divided into categories, based on the type of audio-vestibular side effects (hearing loss, tinnitus, balance disorders and dizziness). Drugs have been further classified based on the target apparatus, therapeutic indications, and pharmacokinetic and pharmacodynamic mechanisms of action. A list in alphabetical order of active principles and trade names has also been prepared for easier consultation.

This guide aims to be a practical, up-to-date and complete tool to rapidly identify the main audio-vestibular side effects of commercially-available drugs. The severity of the audio-vestibular side effects has been classified based on the scale of severity of Adverse Drug Reactions (ADRs) according to Hartwing[84] with a score from 1 to 4.

Hints for Guide Consultation

The guide of audio-vestibular side effects of drugs is composed of three main tables:

- **Supplementary Table I**: list of the active principles divided according to the target apparatus and pharmacological mechanisms of action, with indication of the type of side effect using a number from 1 to 4 (1: ototoxic drugs; 2: drugs inducing tinnitus; 3: drugs inducing vertigo or dizziness; 4: drugs inducing vertigo or dizziness). Sub-lists A1-A2-A3-A4 of table I show the active principles sorted by type of audio-vestibular side effect (A1: ototoxic drugs; A2: drugs inducing tinnitus; A3: drugs inducing vertigo or dizziness; A4: drugs inducing vertigo or dizziness).

- **Supplementary Table II**: list of the active principles in alphabetical order and the relative commercial names with indication of the type of side effect using a number from 1 to 4 (1: ototoxic drugs; 2: drugs inducing tinnitus; 3: drugs inducing vertigo or dizziness; 4: drugs inducing vertigo or dizziness) and the scale of severity according to ADR (a: very common (≥ 10%); b: common (≥ 1% e < 10%); c: uncommon (≥ 0.1% e <1%); d: rare (≥ 0.01% e < 0.1%); e: very rare (< 0.01%); f: unknown).
- **Supplementary Table III**: list of commercial names of drugs in alphabetical order with indication of the type of side effect using a number from 1 to 4 (1: ototoxic drugs; 2: drugs inducing tinnitus; 3: drugs inducing vertigo or dizziness; 4: drugs inducing vertigo or dizziness) and the scale of severity according to ADR (a: very common (≥ 10%); b: common (≥ 1% e < 10%); c: uncommon (≥ 0.1% e <1%); d: rare (≥ 0.01% e < 0.1%); e: very rare (< 0.01%); f: unknown). For each drug, a reference number for the corresponding active principle listed in **Supplementary Table II** has been indicated.

As specified in the table description above, a number has been assigned to each audio-vestibular side effect, as follows:

1) Drugs with explicit reporting by pharmaceutical company and/or health agency as "ototoxic drugs"; these drugs can induce sensorineural hearing loss, with possible association to tinnitus, dizziness and vertigo;

2) Drugs with explicit reporting by pharmaceutical company and/or health agency as "drugs inducing tinnitus"; these drugs can induce tinnitus without effects on hearing and equilibrium;

3) Drugs with explicit reporting by pharmaceutical company and/or health agency as "drugs inducing vertigo or dizziness"; these drugs can induce vertigo and/or dizziness without effects on hearing;

4) Drugs with reporting by pharmaceutical company and/or health agency as "drugs inducing generic hearing disorders"; these drugs can induce generic hearing and/or vestibular disorders without specific ototoxic effects.

Conclusions

The present guide represents an update of the previous guides published by our group on the audio-vestibular side effects of commercially available drugs. General practitioners, otolaryngology, neurology and audiology specialists should be aware of possible audio-vestibular side effects of drugs, such as hearing loss, tinnitus, dizziness and vertigo. The present guide represents a practical tool to rapidly identify potential audio-vestibular side effects of drugs as reported by the pharmaceutical companies and/or health agencies. A periodic update of this guide based on new evidence and reports is necessary.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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