
A Review of Antibiotic-Induced Ototoxicity

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Summary. Ototoxicity is described as the toxicity to the ear: the cochlea, the vestibular system, and the auditory nerve and can be a result of the side effect of a drug. When ototoxicity is caused by drugs, in particular, antibiotics, the degree of damage might vary while the effects can be reversible (temporary) or irreversible (permanent).

Vertigo and hearing loss are the main side effects of ototoxic antibiotics. Vertigo is a false feeling that objects around people are moving while actually they are not. It might be followed by nausea and vomiting, accompanied by nystagmus and ataxia. Hearing loss may range from the inability to hear high-frequency sounds to complete deafness.

Currently, there is not enough information collected about these severe effects that can complicate the use of antibiotics and even disturb patient's daily life.

In this article, we review antibiotic-induced ototoxicity and vertigo effect as well as describe the major agents causing these side effects.

Keywords: ototoxicity, vertigo, antibiotics.

Neurologijos seminarai 2016; 20(69): 135-138

INTRODUCTION

Several different classes of antibiotics have been linked to hearing disorders, vertigo, and tinnitus – together referred to as ototoxic effects of antibiotics [1]. These include aminoglycosides with all compounds linked to a degree of ototoxicity, macrolides, tetracyclines, and glycopeptides. Difficulties concerning assessment and quantification of ototoxicity are one of the reasons for the lack of knowledge about hearing and vestibular disorders among other classes of antibiotics than aminoglycosides [2–4]. There is also a notion that the morbidities such as hearing loss or vertigo caused by antibiotic drugs are not as essential as the life saved by these curing agents [1]. This review is a means to describe the potential ototoxic side effects of the major groups of antibiotics.

WHAT IS OTOTOXICITY?

Ototoxicity can be described as a toxic effect to the inner ear caused by drugs and other chemical agents [1]. The damage can be located in the cochlea, the vestibular system, and the vestibulocochlear (VIII) nerve [5]. Deafness is caused when antibiotic drugs damage the hair cells in the organ of Corti so the sound waves can no longer be converted into action potentials and perceived as sound. By analogy, the receptor hair cells in the vestibular system (in the utricle and saccule) can no longer transmit information

about body positioning when these hair cells are impaired. Bilateral ototoxic damage to the vestibular system often causes no nystagmus or vertigo while in bed or at rest, but these symptoms uncover in everyday life and diminish the quality of life of the patient [6]. This is caused by the loss of integration of information about one's body position and its surroundings as one of the major systems are damaged [7]. It is important to note that hearing loss or diminution occurs independently of vertigo which is associated with ototoxicity [8]. The damage done by antibiotics other than aminoglycosides tends to be reversible, except cases of bigger dosages, patients with renal impairment or other associated underlying conditions.

MECHANISM OF OTOTOXICITY

The mechanisms that are responsible for ototoxic effects of antibiotics are still in need to be studied as only one group of antibiotics – aminoglycosides – was considered more extensively. Hearing loss has been associated with the accumulation of aminoglycosides in hair cells as demonstrated by the animal study of fluorescent gentamicin [9]. Gentamicin's accumulation in the perilymph and endolymph was noted as well [4]. As increased aminoglycoside concentrations in fluids bathing bullfrog's saccule receptor hair cells were shown to block receptor signals by interacting with transduction channels, this could be a part of the vestibular damage mechanism caused by aminoglycosides [10]. Vestibulotoxicity includes damage to both type I and II hair cells with type I being more susceptible. It is interesting to note that ototoxic aminoglycosides tend to damage the base of the cochlea first and only then impair receptor cells up to the apex [11]. As the reception of sound is arranged according to the frequencies of sound

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waves (tonotopically), the disturbance caused by aminoglycosides first occurs in high-frequency receptor cells [6, 12]. However, the accumulative cellular effect is not considered to be a major pathway of ototoxicity, its importance remains controversial [1]. Aminoglycosides were also shown to induce apoptosis of sensory cells and increase the amount of reactive oxygen species (ROS) causing cellular damage [13–17]. The outer hair cells are more susceptible to damage [18]. The role of ROS is also substantiated in an animal study involving NF-E2-related factor (Nrf2) knockout mice which showed more severe ototoxicity after gentamicin treatment as the gene for producing antioxidant enzymes was knocked-out [19]. Clinical use of antioxidants in preventing ototoxicity remains controversial [1]. Mitochondrial rRNR mutations are also considered as one of the factors of aminoglycoside ototoxicity [4]. The second involvement of mitochondria in the mechanism of ototoxicity is the release of the pro-apoptotic factors after the increase of membrane permeability due to possible activation of aminoglycoside-induced c-Jun N-terminal kinase (JNK) cascade or by a similar MAP kinase pathway finally leading to apoptosis. Aminoglycoside (gentamicin) ototoxicity was noted to follow both caspase-dependent and caspase-independent pathways [18].

OTOTOXICITY IN DIFFERENT CLASSES OF ANTIBIOTICS

Macrolides

Erythromycin has been suspected as an ototoxic agent in high dosages (1 g every 6 hours), however, hearing loss tends to be reversible except some cases [20, 21]. Treatment preceded by hepatic or renal impairment is also linked to ototoxic side effects, such as hearing loss or dysfunction, tinnitus, and vertigo due to possibly decreased clearance or slower metabolism [22]. Azithromycin is associated with hearing loss only during prolonged high-dose treatment [22–24]. This macrolide antibiotic was designed to have less ototoxic effects than erythromycin and is considered safer [25].

Tetracyclines

Minocycline was noted to cause transient vertigo, ataxia, nausea, and tinnitus with doses as small as 100 mg. The first ototoxic symptoms tend to occur up to 72 hours after taking the drug. As minocycline is used for meningococcal prophylaxis, a dosage of 200 mg initially followed by 100 mg twice a day for three days was shown by Munford et al to be effective, with an incidence of side-effects of 18.4% [26]. Incidence of minocycline ototoxicity has been observed to be bigger in women than men [27].

Glycopeptides

Vancomycin, often used as a treatment for methicillin-resistant *Staphylococcus aureus*, has been linked to reversible ototoxicity following concentrations >40 mg/L and irreversible damage with concentrations >80 mg/L or preex-

isting renal impairment [28]. Recommended vancomycin concentrations range from 30–40 mg/L to 5–10 mg/L. Vancomycin ototoxicity was also questioned as enhancing the damage caused by other antibiotics, such as aminoglycosides, however, certainty is lacking [12, 20]. Vancomycin is associated with hearing loss, tinnitus, and dizziness [20, 29]. The age of the patient can be a factor to vancomycin-induced ototoxicity as well, with older patients being more susceptible, however, more data is needed to confirm [30]. The safety of vancomycin use during pregnancy is to be resolved [31].

Aminoglycosides

Aminoglycosides cause irreversible hearing loss and vestibular damage often with dominant hearing loss as noted for kanamycin, neomycin, amikacin, and netilmicin or vestibular dysfunction, prominent with use of streptomycin, tobramycin, and gentamicin: “Neomycin is considered the most highly toxic; followed by gentamicin, kanamycin, and tobramycin; while amikacin and netilmicin are considered the least toxic. Amikacin, neomycin, and dihydrostreptomycin tend to be more cochleotopic while gentamicin and streptomycin are more likely to target the vestibular sensory epithelium” [32–34]. Cases of streptomycin ototoxicity tend to increase with prolonged and high dosage and decrease with intermittent dosage [35]. However, there are stipulations that only cumulative effects cause major differences in toxic effects among patients [8]. Renal impairment and the age of the patient are important factors when considering both use and dosage of aminoglycosides, including streptomycin [36]. Symptoms include hearing loss that is permanent or vestibular dysfunction including ataxia, dizziness, and nystagmus [32]. Vestibular impairment was noted in 27.97% of cases in a study of 143 tuberculosis patients [37]. Symptoms of hearing loss when using dihydrostreptomycin sulfate are often seen only 1 to 6 months after treatment [36]. As streptomycin use has become minimal in the clinical setting, it serves as a model compound to track the possible ototoxic effects of other aminoglycosides. Kanamycin is advised in dosages 15 mg/kg/d and the total dose should not exceed 40 g in order to maintain a low risk of cochlear degeneration [38, 39]. Topical use of tobramycin is safe because of low systemic concentration, however, inhalant use should be considered as potentially ototoxic when the patient in need has renal impairment. Though low serum concentrations (1 mcg/ml) are not considered dangerous, transient tinnitus is sometimes reported [1]. A single dose of 5–7 mg/kg of gentamicin or tobramycin (and 15 mg/kg) is advised when creatinine clearance is >60 ml/min. If creatinine clearance is smaller the dose should be reduced [40].

DETECTION AND PREVENTATIVE MEASURES

Patient evaluation and screening during treatment with potentially ototoxic antibiotics are recommended; high-frequency audiometry is the test of choice [1, 41, 42]. Early

detection of high-frequency (8 kHz) hearing impairment can help physicians decide whether the treatment used is convenient [43]. Audiometric monitoring has recently increased in cystic fibrosis units in the United Kingdom and such practice should be recommended when using potentially ototoxic agents [44]. Regular tests preventing life-long impairment are sometimes not acknowledged because of a primary, life-threatening infection which hinders appreciation of the need to preserve hearing [43].

CONCLUSIONS

The understanding of antibiotic-induced ototoxicity and vertigo is limited and more experimental data in animal models is required in order to understand the possible threat and mechanisms of the development of these side effects. Additional care must be taken when prescribing antibiotics to elder patients, those with hearing or vestibular dysfunction as well as ones with renal impairment. Physicians should be aware of ototoxicity when considering prolonged treatment and high doses of potentially harmful antibiotics as well as the accumulation of such agents in the tissues of the cochlea and vestibular system. The evaluation of hearing or the inquiry about episodes of dizziness, tinnitus, or nausea reported by the patient during or after treatment could be a helpful way to collect more data about ototoxic agents, especially about antibiotics other than the widely-researched aminoglycosides.

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ANTIBIOTIKŲ SUKELTO OTOTOKSIŠKUMO APŽVALGA

Santrauka

Ototoksiškumas yra apibūdinamas kaip toksikiškumas ausiai ar jos dalims: sraigei, vestibulinei sistemai, klausos nervui, ir gali būti vaisto šalutinis poveikis. Kai ototoksiškumą sukelia vaistai, padaryta žala gali skirtis, o poveikis gali būti grįžtamas (laikinas) arba negrįžtamas (nuolatinis).

Pagrindiniai ototoksinių antibiotikų šalutiniai poveikiai – galvos svaigimas ir klausos sutrikimas. Galvos svaigimas (vertigo) – klaidingas žmogaus aplinkos judėjimo pojūtis, dažnai siejamas su pykinimu, vėmimu, vaikščiojimo ir koordinacijos sutrikimais (ataksija), nistagmu. Klausos sutrikimai, sukelti kai kurių antibiotikų, įvairuoja nuo nesugebėjimo išgirsti aukštesnių dažnių iki visiško kurtumo.

Šiuo metu nėra pakankamai informacijos apie minėtus reiškinius ir antibiotikų įtaką jų išsivystymui, tačiau šie šalutiniai poveikiai gali apsunkinti antibiotikų skyrimą ar net sutrikdyti paciento kasdienį gyvenimą.

Šiame straipsnyje apžvelgsime antibiotikų sukeltą ototoksiškumą ir galvos svaigimą, pagrindines šiuos simptomus sukeliančias medžiagas.

Raktažodžiai: ototoksiškumas, galvos svaigimas, antibiotikai.

Gauta:
2016 08 08

Primta spaudai:
2016 08 24