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Amikacin Ototoxicity: Case Report and Literature Review

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Abstract

Introduction: Aminoglycosides are ototoxic drugs for their potential to cause irreversible damage to inner ear structures. They are used for aerobic Gram negative bacterial infections or as second line therapy for pulmonary tuberculosis.

Case Report: A 44-year-old male patient in the 4th month of therapy for pulmonary tuberculosis with a second line regimen with levofloxacin, ethambutol and amikacin, presents at the ENT department with bilateral progressive hearing loss. Audiogram revealed deep right and severe left sensorineural hearing loss. Potential ototoxicity was assumed for amikacin, which was discontinued. The patient maintained follow-up with serial audiograms and was proposed for hearing rehabilitation.

Discussion: Amikacin is used as second line therapy in pulmonary tuberculosis, and ototoxicity may occur after several weeks or months of its use, as in the present case. Hearing loss is irreversible most of the time, and audiometric monitoring is preponderant before, during and after therapy. A short literature review is carried out on the mechanisms of ototoxicity of these drugs, their prevention and monitoring.

Keywords:

Amikacin; Ototoxicity; Aminoglycosides; Hearing loss; Pulmonary tuberculosis

Introduction

Ototoxic drugs are those that have the potential to cause cellular damage in the inner ear, leading to vestibular and cochlear function losses, mostly irreversible. Some of these drugs include aminoglycoside antibiotics, anti-neoplastic agents, salicylates, quinine and loopdiuretics [1,2]. Aminoglycosides are used for aerobic gram-negative bacterial infections in the empirical treatment of severe infections such as septicemia, respiratory, urinary and gastrointestinal tract infections, neonatal sepsis, or as second-line tuberculosis therapy [3,4]. Ototoxicity is a relevant side effect given the regular use of these antibiotics in clinical practice [3,5]. The prevalence of pulmonary tuberculosis is still significant in Portugal [6]. Injectable aminoglycosides are used as second-line therapy in combination with other tuberculostatic drugs in resistant pulmonary tuberculosis or in cases of impossibility of using first-line drugs for other individualized contraindications [7]. The onset of ototoxicity varies with the duration, doses and treatment regimens, and may occur after several weeks or months of its use or even after its completion [4]. We report the case of a patient with resistant pulmonary tuberculosis under treatment with amikacin, who developed ototoxicity manifested by bilateral sensorineural hearing loss.

Case Report

A 44-year-old male patient with alcoholic liver cirrhosis treated with furosemide and spironolactone was diagnosed with pulmonary tuberculosis, resistant to isoniazide. He started traditional tuberculostatic therapy, however suspended for hepatic toxicity, and then started a second line treatment with levofloxacin, ethambutol and amikacin. At the 4th month of therapy he developed tinnitus and progressive bilateral hearing loss, and for these complaints was observed at the ENT department. The clinical examination showed normal otoscopy. He performed an audiogram that revealed mild bilateral sensorineural hearing loss. Given the reference to previous normal hearing, amikacyn ototoxicity was suspected, which was stoped after discussion with pneumology team. The audiometric reassessment after 15 days showed sensorineural hearing loss progression. He maintained tuberculostatic therapy with levofloxacin and ethambutol and discontinued therapy with furosemide. The audiometric reevaluation 2 months after amikacin cessation revealed left hearing loss progression. The patient was proposed for hearing rehabilitation.

Discussion

The first known aminoglycoside was streptomycin, isolated from Streptomyces griseus, and proved to be an effective antibiotic therapy for aerobic gram-negative bacterial infections and tuberculosis [3]. In the subsequent years, other aminoglycosides were isolated from the same specimen, and currently nine of these FDA-approved clinical drugs are used: streptomycin, neomycin, tobramycin, kanamycin, paramomycin, spectinomycin, gentamicin, netilmicin and amikacin [3]. Shortly after its discovery, its capacity for cochlear and vestibular toxicity was detected and showed in clinical studies, in addition to nephrotoxicity [4]. Currently, amikacin, kanamycin and capreomycin are used as second line therapy in pulmonary tuberculosis [7].

Ototoxicity Mechanisms

All aminoglycosides have ototoxic potential, despite different affinities for the cochlear or vestibular epithelium [5]. Among them, streptomycin and gentamicin are predominantly vestibulotoxic, whereas amikacin, neomycin, kanamycin and capreomycin are predominantly coclotoxic [1].

Aminoglycosides have bactericidal action by binding to the 16S rRNA of small (30S) bacterial ribosomal subunits causing translation errors leading to inhibition of protein synthesis and apoptosis. Its lower affinity for eukaryotic cells determines its bacterial specificity [8]. However, aminoglycosides can penetrate cochlear and vestibular hair cells by a mechanotransduction channel, reaching higher concentrations than in the other cells of the organism [8]. Once within hair cell, they act by several molecular mechanisms leading to oxidative stress, excitotoxicity, protein synthesis inhibition and mitochondrial dysfunction with apoptosis [3].

In the vestibular system, cellular damage begins at the apical region of the crista ampularis and maculae and can extend to peripheral regions of the sensitive epithelium, first affecting type I hair cells [4]. Cochlear toxicity begins in the basal turn of the cochlea, with a preference for external hair cells, similarly to acoustic trauma and presbycusis [9,10], and there may be progressive destruction of the spiral ganglion cells [4]. As a result, hearing loss begins at high frequencies and can be detected by high-frequency audiometry before it becomes symptomatic [3]. As the high-frequency spectrum is not routinely used in audiometric tests (>8 KHz), the true incidence of ototoxicity is generally underestimated [3]. With continued exposure, the damage extends to lower frequencies reaching the spectrum of speech.

Ototoxicity causes sensorineural hearing loss, tinnitus or loss of speech discrimination [1]. It is usually audiometrically defined as losses of 20 dB at a frequency, or losses of 10 dB at two or more contiguous frequencies or loss of response at three consecutive frequencies relative to a baseline audiogram [11]. Vestibular toxicity is usually bilateral and symmetrical and manifests as symptoms of dizziness, imbalance, or oscillopsia [12].

Ototoxicity may occur after days or weeks of aminoglycoside therapy. It correlates with the total dose received and with the longest exposure to therapy [4], and is usually irreversible. Studies have demonstrated progression of hearing loss even after

6 months of aminoglicoside cessation [13]. Other risk factors that interfere with the ototoxicity threshold, such as age, genetic mutations or the concomitant use of other ototoxic drugs also contribute to this [1,3].

In the present case, sensorineural hearing loss occurred after 4 months of therapy, and its progression was verified even after its cessation, which corroborates what has been described in the literature. As a risk factor for the development of ototoxicity, concomitant use of furosemide, a potentially ototoxic drug, may also have contributed.

Aminoglycosides in Pulmonary Tuberculosis

Pulmonary tuberculosis is still a prevalent disease in Portugal [6]. Aminoglycosides are used as second-line drugs in cases of resistant pulmonary tuberculosis or when first-line drugs are contraindicated for individual reasons [7]. According to the World Health Organization, multidrug-resistant pulmonary tuberculosis has been increasing in recent years, and international guidelines recommend a 20-month course of combination treatment. In this context, the use of aminoglycosides raises the problem of ototoxicity. In the case of aminoglycosides, the recommendations stipulate the choice of amikacin, kanamycin or capreomycin. All these agents are administered in injectable form, suggesting a treatment course of at least 8 months [7].

The problem of ototoxicity is known early with the use of these drugs, especially for long term treatment, and is generally irreversible [13]. The incidence of ototoxicity is variable and has led to several studies, and for this variability many factors contribute, like the type of aminoglycoside used, risk factors inherent to the patient, therapeutic schemes and the audiometric monitoring and different definitions of ototoxicity.

In this context, studies about aminoglycoside ototoxicity during pulmonary tuberculosis treatment reported incidences between 18% and 42%, defining ototoxicity by clinical and audiometric criteria-losses of 20 dB at a frequency or 10 dB at two adjacent frequencies [13-16].

Another frequently raised issue is the relationship between the occurrence of ototoxicity and the therapeutic regimens of daily or weekly doses, serum concentrations and duration of therapy. The recommended doses are 15 mg/kg. In the treatment of mycobacterial diseases, aminoglycosides can be used in daily, twice weekly or third weekly regimens [15].

In fact, some studies have shown that ototoxicity is unrelated to the daily versus weekly dose regimen [15]. Several studies have also found that ototoxicity is more related to the total dose received and the longer exposure to therapy than serum aminoglycosides levels [15,17] and are against a limitation of maximum daily doses of 1000 mg, suggesting that this limitation may lead to a longer therapy course with a higher risk of ototoxicity [15].

As to the ototoxicity potential of the different aminoglycosides, a linear definition is not possible given the differences in variables considered in the different studies - the risk factors inherent to the patient, the schemes used and which aminoglycosides are compared - but Sturdy et al. suggest that capreomycin may have a lower ototoxic effect than amikacin, and a study on the occurrence of ototoxicity in the treatment of pulmonary tuberculosis comparing amikacin, kanamycin and streptomycin with similar doses and duration of treatment has suggested that these drugs have similar but not identical patterns of ototoxicity [14,15].

Audiometric monitoring is not always performed in these patients, some studies demonstrating that only half of the patients treated were screening with audiogram [14]. In the present presented, audiometric monitoring was not performed at the start of therapy, which demonstrates that ototoxicity screening is not always achieved. This monitoring is important since cellular damage can occur before becoming symptomatic as it starts at high frequencies, and it’s important to change therapeutic regimen as soon as possible to prevent a progression of hearing loss [13,14]. Despite therapy discontinuation, hearing loss may progress, even after 6 months of its completion [5,13].

Ototoxicity Prevention Targets

Several animal studies have been conducted to investigate the action of various drugs and molecules on aminoglycosides targets in the cochlear system and their utility for preventing or treating ototoxicity. However, these studies are done in vitro or in vivo in animals, and to date there's no data on their efficacy in humans. Even so, the discovery of drugs with the potential to prevent aminoglycoside-induced cell death opens the way to new strategies for preventing ototoxicity.

Sorafenib is an antineoplastic drug inhibiting multiple kinases such as Raf, VEGFR and other relevant in tumor proliferation kinases [8]. It has been postulated that in hair cell, aminoglycosides bind to rRNA and lead to protein synthesis inhibition by activation of the c-jun pathway (JNK). It was demonstrated in an animal study that Sorafenib can inhibit the activation of the JNK pathway by aminoglycosides, constituting a potential mechanism to prevent ototoxicity [8]. One of the mechanisms of cellular toxicity is the formation of iron complexes with gentamicin with production of oxygen free radicals that lead to mitochondrial dysfunction. It has been shown in an animal study that coenzyme Q-ter-a soluble form of coenzyme Q-interferes in this mechanism of oxygen free radical generation and may be useful in the protection of outer hair cells [9]. Other drugs have also shown potential for preventing ototoxicity in animal studies, such as acetylsalicylic acid, NMDA receptor antagonists and anti-oxidants, but to date it has not been proven to prevent ototoxicity *in vivo* [3].

Prevention and Monitoring

Some guidelines recommend serum aminoglycoside levels monitoring during its use, but several studies have shown that ototoxicity does not correlate with this parameter, but with the total dose received and the longer time of exposure to therapy [4].

According to the American Speech-Language-Hearing Association, it is recommended to perform an audiogram before starting therapy with ototoxic drugs, such as aminoglycosides; during therapy 1 to 2 times a week, and up to 6 months after its completion. The cessation or, if possible, substitution of therapy, taking into account the benefit-risk, is also recommended when cochleo-vestibular toxicity is detected [11].

When hearing loss is irreversible, the use of prosthetic adaptation or cochlear implant is an option for auditory rehabilitation.

Conclusion

Amicacin, as well as other aminoglycosides, are ototoxic drugs used in clinical practice, namely as second-line treatment of pulmonary tuberculosis, as in the present case. The irreversible cochlear damage raises the importance of detecting individual ototoxicity risk factors and auditory function monitoring when its use is weighted. Once hearing loss is established, therapy reassessment with its substitution and, if possible, cessation may be considered, and auditory rehabilitation may be offered.

Conflict of Interest

None.

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