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Literature Review

Toxicity in the vestibular system: A literature review

Abstract

The objective of this study was to systematically review the bibliographies dealing with vestibular toxicity, its morphological and functional damages. This review was carried out with a search in the electronic databases Virtual Health Library (VHL), Medical Literature Analysis and Retrieval System Online (MedLine) with the tool PubMed, Latin American and Caribbean Literature in Health Sciences (LILACS) and Scientific Electronic Library Online (SciELO), from October to November / 2018. As a search strategy, the following keywords were used in Portuguese and their correspondents in English and Spanish: vestibular toxicity, vestibular ototoxicity and vestibulotoxicity. A total of 265 complete articles were collected in the databases searched. Of these, after the analysis, thirteen articles and a master's thesis were used. Articles range from 1977 to 2017, mostly involving American researchers. The toxicity of aminoglycoside antibiotics was the predominant issue, but other substances were also reported in less number. Most of the studies used as sample the experimental model. Predominant were studies whose substance searched had confirmed vestibulotoxicity.

Introduction

Ototoxicity is defined as a partial or total loss of vestibular and / or cochlear function as a consequence of the use of drugs, usually these are administered for therapeutic purposes or exposure to toxic substances. The degree of severity of intoxication depends on the individual predisposition, the dose administered, the duration of treatment, the route of administration, the age of the patient, the family tendency and / or any previous damage to the inner ear [1].

Ototoxic damage may initially be reversible, but the type of agent and the dose administered are determinants for the reversibility of the injury. Aminoglycoside antibiotics, which are the most common causes of drug-induced ototoxicity, usually produce permanent damage [2].

An ototoxic agent is defined as a substance, a chemical or a drug that causes functional damage or cellular damage to the inner ear, especially at the cochlear level and / or semicircular canals and the VIII cranial nerve [3].

Certain medications have the ability to cause damage to the inner ear. Potentially ototoxic drugs are antibiotics of the group of aminoglycosides (gentamicin, neomycin, kanamycin, among others), vancomycin, viomycin, furosemide, ethacrynic acid, nitrogen mustard, quinine, salicylates [4], among others.

Ototoxicity has been known since the 19th century when it was found that drugs like quinine and salicylic acid could produce temporary change in auditory threshold as well as dizziness and tinnitus. However, ototoxicity was only recognized as a real medical problem in the twentieth century. In the 1940s (20th century), patients treated with streptomycin, a drug used in tuberculosis therapy, had permanent lesions of the vestibular and cochlear organs [5].

Research strategy

This review was carried out with a search in the electronic databases Virtual Health Library (VHL), Medical Literature Analysis and Retrieval System Online (MedLine) with the tool PubMed, Latin American and Caribbean Literature in Health Sciences (LILACS) and Scientific Electronic Library Online (SciELO), from October to November, 2018.

As a search strategy, the following keywords were used in Portuguese and their correspondents in English and Spanish: vestibular toxicity, vestibular ototoxicity and vestibulotoxicity. There was no temporal restriction.

The analysis and selection of the files were performed by two independent researchers and, later, the data were crossed for closure.

Selection criteria

To be included in the research, studies should be original

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articles (excluding other revisions), be available in full in the database, address in their theme the toxicity of a substance in the vestibular system.

Data analysis

The articles found with the search in the databases were initially selected by the title and those that did not fit the theme of this review were immediately excluded. In the following moment, the abstracts were read, where no article was excluded, and then the entire publication was read for later analysis and selection of the information.

A total of 265 complete articles were collected in the databases searched. Of these, 206 were initially excluded by the title. Of the 59 remaining articles, in 12 of them the complete text was not found at the address indicated and there were 32 reprints of articles between the databases.

After the analyzes, 13 articles and a master's thesis were included in the present study. For each included study, the following information was cataloged: main author, year of publication, country of origin of the investigators, sample and substance used (Table 1).

In the collection of information, only the data referring to the vestibular system were considered for the articles that did not deal with this theme alone.

Table 1: Framework 1.

Primary author	Year of publication	Country of origin	Sample	Substance used
Christensen	1977	USA.	Gatos	Amicacin and Gentamicin
Dulon	1986	France and U.S.A.	Guinea pig	Gentamicin, Netilmicina and Amicacina
Lima	2003	Brazil	Humans	Streptomycin
Lyford-Pie	2007	USA.	Chinchilas	Gentamicin
Star	2008	Brazil	Humans	Organofosforados
Roth	2008	USA.	Humans	Gentamicin
Kawamoto	2009	USA.	Mice	Gentamicin
Kim	2009	Korea	Ratos	Gentamicin
Pisarik	2009	USA.	Humans	Aspartame
Massuda	2009	Brazil	Guinea pigs	Biosilicato
Körbes	2010	Brazil	Guinea pigs	Organofosforado
Schleker	2011	USA.	Mice	Nitrile compound
Liu	2011	USA and China	Rats	Etacrinic Acid and Kanamycin
Deutschmann	2017	Brazil	Humans	Platinum Derivatives

Results

As the search for articles happened without temporal restriction, there was an extensive time interval between searches. The oldest study found was published in 1977 [7], and the most recent, published in 2017 [8].

Approximately 57% of the studies found were published in the last decade [9-19]. Of these, only one has been published in the last five years [8], which confirms the need for conducting up-to-date research on vestibular system toxicity.

Most of the studies involve American researchers (57%), followed by Brazilians with 35.7%, and only one Korean study was found. French and Chinese researchers appear as partners for Americans, each in a separate study. These findings demonstrate that the United States is the country that has been promoting its publications in vestibular toxicity studies.

Analyzing the studies taking into account the sample, the use of animal models prevailed. In 64.3% of the studies, a model of animal experimentation was used [7,9,11-13,17-20], of which almost 90% were rodents (guinea pig, mouse, rat and chinchilla) [11,14,15,17-20]. Only one study used a feline model [7].

A survey conducted in electronic databases revealed that 85% of the articles published in Medline and 70.5% in LILACS over a four-year period used rodents [21], which shows that research in experimental models is a a recurring tool in current studies due to ethical problems and the collection of biological material in human research.

Considering the area of auditory research, the model of animal experimentation is frequently used, mainly guinea pigs and rats due to the ease of handling of the animals and the anatomical similarity with the human ear [22].

An important point to note when analyzing animal research is the interpretation of the results, that is, the difference between the dimensions of the human auditory structures and the dimensions of the auditory structures of the experimental animals should be considered [23].

The studies included in this study are mainly concerned with research involving aminoglycoside antibiotics [7-11,13-15,20]. Of these antibiotics, amikacin, gentamicin, netilmicin, streptomycin and kanamycin were investigated. Among the aminoglycosides, gentamicin was the most recurrent in the studies [7,11,13-15,20], appearing isolated [11,13-15] ,or in combination with other drugs [7,20]. Other substances analyzed in the studies were: derivatives of platinum [8], ethacrynic acid [9], aspartame [16], biosilicate [17], organophosphorus compounds [18] and a nitrile component [19].

Aminoglycosides are the drugs with the most known ototoxicity studied, with streptomycin being the first to have its proven ototoxicity. The frequent use of these antibiotics is due to its low cost and good effectiveness, although it presents ototoxicity as a side effect [24].

Aminoglycosides are a group of antibiotics with complex chemical structure, resembling one another in antimicrobial activity, pharmacokinetic characteristics and toxicity. The main agents are gentamicin, streptomycin, amikacin, tobramycin, netilmicin and neomycin [6].

This type of antibiotic is effective against many gram-

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negative and gram-positive microorganisms. They are widely used against gram-negative enteric microorganisms and in sepsis [25]. Such antibiotics have well-known side effects, the most important of which are nephrotic and ototoxicity [6].

Aminoglycosides, such as streptomycin, gentamicin and tobramycin, have a greater effect on the vestibular than on the auditory apparatus, that is, they are more vestibulotoxic than cochleotoxic. Others such as netilmicin, neomycin, kanamycin and aminosidine have greater cochleotoxic action [26]. Researchers state that any aminoglycoside can produce both types of effect, but streptomycin and gentamicin are more likely to interfere with vestibular function, whereas neomycin and amikacin preferentially affect hearing [27].

Although the aminoglycoside gentamicin is the most researched compound at present, which proves that this class of antibiotics has strong vestibulotoxic power. Other substances are being studied to allow greater clarification about their toxicity to the vestibular system.

Conclusion

Considering the results presented, it can be seen that vestibulotoxicity is a highly relevant research question. Studies indicate that aminoglycoside antibiotics are the major cause of vestibular toxicity and are also the most investigated substances for their frequent and low cost use. However, other substances such as aspartame, organophosphates, among others, have been studied and have also been demonstrated with vestibulotoxic power.

It is suggested to expand the studies with other potentially vestibulotóxicos substances, as well as to deepen the researches with those already recognized, so that one can prevent the damage caused to the vestibular system, often irreversible; and treat it when possible.

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