

CASE REPORT

FIRST REPORT ON OTOTOXICITY OF MEGGLUMINE ANTIMONIATE

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SUMMARY

Introduction: Pentavalent antimonials are the first drug of choice in the treatment of tegumentary leishmaniasis. Data on ototoxicity related with such drugs is scarcely available in literature, leading us to develop a study on cochleovestibular functions. **Case Report:** A case of a tegumentary leishmaniasis patient, a 78-year-old man who presented a substantial increase in auditory threshold with tinnitus and severe rotatory dizziness during the treatment with meglumine antimoniate, is reported. These symptoms worsened in two weeks after treatment was interrupted. **Conclusion:** Dizziness and tinnitus had already been related to meglumine antimoniate. However, this is the first well documented case of cochlear-vestibular toxicity related to meglumine antimoniate.

KEYWORDS: Mucocutaneous Leishmaniasis; Drug Toxicity; Meglumine antimoniate; Hearing loss; Tinnitus; Dizziness.

INTRODUCTION

Pentavalent antimonials are still the first drug of choice in the treatment of tegumentary leishmaniasis (TL), although they can cause adverse reactions such as electrocardiographic, liver, pancreas and kidney function alterations⁴. Myalgia, arthralgia and fever are common and vestibular alterations such as dizziness are occasionally observed^{2,12}. However, we could not find any well documented report on cochlear and vestibular toxicity caused by meglumine antimoniate.

The present case report of ototoxicity of meglumine antimoniate (MA) was diagnosed during an ongoing longitudinal study in patients with TL treated at IPEC-FIOCRUZ, Rio de Janeiro, Brazil. All patients were submitted to vestibular evaluation (Vectoelectronystagmography - VENG) and audiologic evaluation (conventional pure tone audiometry, distortion product otoacoustic emissions - DPOAE and tympanogram) before, during (every ten days) and up to three months after treatment discontinuation or normalization of alterations. During the monitoring process, patients were submitted to physical examination, blood biochemistry, complete blood count and ECG. The normal values of the laboratory tests were: glucose (70-110 mg/dL); urea (15-38 mg/dL); creatinine (0.6-1.3 mg/dL); amylase (25-115 mg/dL); lipase (114-286 mg/dL); aspartate transaminase (AST) (15-37 U/L); alanine transaminase (ALT) (12-78 U/L); alkaline phosphatase (ALP) (50-136 U/L); gamma glutamyl transpeptidase (GGT) 15-85 U/L.

Ototoxicity was considered the onset of dizziness and/or hearing loss (with a unilateral or bilateral audiometric threshold increase equal to or greater than 20 dB, at one or more frequencies, or a 10dB increase at two adjacent frequencies) during treatment with meglumine antimoniate^{1,6}.

This study was submitted to and approved by the Research on Human Beings Ethics Committee of the Evandro Chagas Research Institute of the Oswaldo Cruz Foundation (IPEC- FIOCRUZ), under the number 0055.0.009.000-07. The patient agreed to participate in the study and signed a free informed consent form.

CASE REPORT

A seventy-eight year-old man, without previous skin lesions or skin scars consistent with tegumentary leishmaniasis (TL), evolved during the last year with volume increase in the nasal pyramid to the right side, nasal obstruction, epistaxis to manipulation of nasal cavities, crusting and occasional cacosmia. He also had 117 mg/dL glucose; 48 mg/dL urea; 1.5 mg/dL creatinine; 78 mg/dL amylase; 22 U/L AST; 30 U/L ALT; 74 U/L ALP. Systemic arterial hypertension was treated with 25 mg/day hydrochlorothiazide 20 mg/day nifedipine, 2 mg/day doxazosin mesylate, besides 50 mg SOS sodium diclofenac, due to chronic muscle pain. He reported bilateral hearing loss for the last seven years, but he denied tinnitus, dizziness, noise exposure or family history of auditory and/or vestibular symptoms. Otoscopy was normal and the endoscopic

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examination of the upper aero-digestive tract presented infiltration of the right nasal wing and the entire mucosa of the right nasal cavity, preventing progression of optics. There was also infiltration of the vestibular region, anterior nasal septum and head of the left inferior turbinate, with discrete crusts, as well as absence of mucosal lesions in the pharynx and larynx. Syphilis and fungal serologies were negative. TL serologies performed were: 1:40 indirect immunofluorescence technique and ELISA reactor. A nasal biopsy was performed. Fragment cultures were negative to *Leishmania*, mycobacteria and fungus. The histopathological examination revealed chronic granulomatous inflammation with necrosis. The immunohistochemistry with anti-*Leishmania* serum showed occasional amastigote forms and polymerase chain reaction was positive to *Leishmania*. A pre-treatment audiometric study showed mild to severe sensorineural hearing loss, tritone mean at 500-1000-2000 Hz of 53dB and 62dB, in the right and left ears, respectively. Additionally, he presented bilateral type A tympanogram and bilaterally absent distortion product otoacoustic emissions (DPOAE). Treatment with meglumine antimoniate (MA) (Glucantime® from Sanofi Aventis) was initiated at a maximum daily dose of three ampoules (weight 72 kg; dose 16.9 mgSb⁵/kg/day) for 30 days.

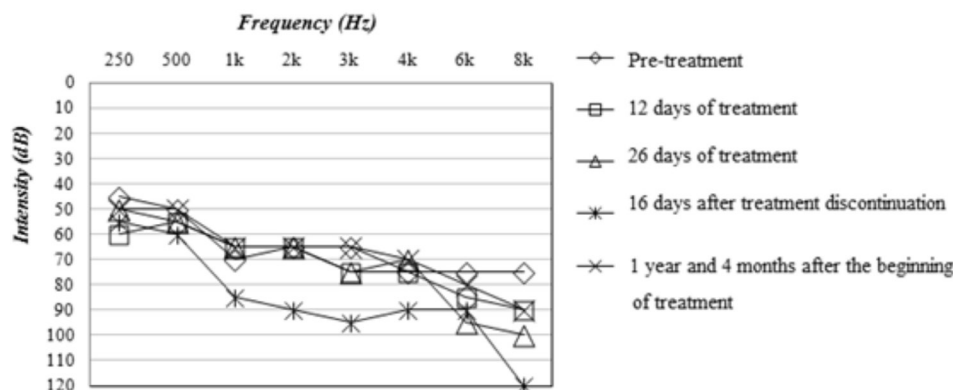
On the twelfth day of treatment, the patient returned with herpes zoster in the buttock (dermatome S1) and myalgia, and acyclovir cream, urea cream and 50 mg of sodium diclofenac if pain were prescribed. He was asymptomatic from the cochlea-vestibular point of view, but presented a 10 dB increase of the auditory threshold at 6 kHz and a 15 dB increase at 8 kHz in the left ear (LE). On the twenty-sixth day, treatment was discontinued due to cutaneous rash, scaling of lower limbs, difficulty in walking, arthralgia, myalgia, hand tremor, dry oral mucosa, anorexia and loss of weight (-3 kg). He also presented frequent severe rotatory dizziness lasting some minutes with no associated vagal symptoms, without worsening of hearing complaints previously reported. VENG was normal and the audiometry showed a 20 dB increase at 6 KHz and a 25 dB increase at 8 KHz in the LE. He also had 153 mg/dL glucose; 83 mg/dL urea; 322 mg/dL amylase; 181 U/L AST; 174 U/L ALT; 112 U/L ALP; 175 U/L GGT) and QTc 0.46. Sixteen days after the treatment was discontinued, he maintained rare non-rotatory dizziness lasting seconds, without objective worsening of hearing complaints, but with tinnitus, and he had fallen two days before. Pure tone audiometry presented severe worsening of LE auditory thresholds (10 dB increase at 250 Hz; 10 dB increase at 500 Hz; 15 dB increase at 1 KHz; 25 dB increase at 2 KHz; 30 dB increase at 3 KHz; 15 dB increase at 6 KHz; and 45 dB increase at

8 KHz) and VENG was within the normal range, although with reduction of more than 50% of the previous value of Angular Velocity of the Slow Component of Nystagmus in degrees per second (AVSC %/s) at 18 °C. He had 118 mg/dL glucose; 30 mg/dL urea; 90 mg/dL amylase; 41 U/L AST; 71 U/L ALT; 155 U/L ALP; 128 U/L GGT) and QTc 0.33. Twenty-eight days after treatment interruption, he no longer had tinnitus and dizziness remained of mild intensity and lasting seconds. He walked adequately and myalgia and tremors had improved. Pure audiometry showed no more increments consistent with ototoxicity criterion. He had 110 mg/dL glucose; 1.4 mg/dL creatinine; 105 mg/dL amylase; 371 mg/dL lypase; 34 U/L AST; 43 U/L ALT; 115 U/L ALP; 80 U/L GGT) and QTc 0.33. As the patient still presented mucosa lesions 90 days after treatment interruption, he was successfully treated with 150 mg/day (2.2 mg/kg/day) liposomal amphotericin B, up to an accumulated dose of 1800 mg, when it was discontinued due to serum creatinine value of 1.6 mg/dL, without worsening of hearing and/or dizziness complaints. A year and four months later, he did not present worsening of hearing complaints when compared to the beginning of treatment with MA, neither tinnitus nor dizziness, and the audiometry was not consistent with ototoxicity criterion and VENG was within the normal range, with AVSC in the LE at 18 °C returning to values similar to the beginning of symptomatology. The DPOAE examination remained absent during the entire monitoring. Graphs 1 (Pure tone audiometry through air conduction of the left ear of a patient during the monitoring process, IPEC, FioCruz, Rio de Janeiro, 2011) and 2 (Variations of Angular Velocity of the Slow Component of Nystagmus in degrees per second (AVSC %/s) of the patient during the monitoring process - IPEC, FioCruz, Rio de Janeiro, 2011) show the variations in pure tone audiometry and of the angular velocity of the slow component of nystagmus, during the patient's follow-up.

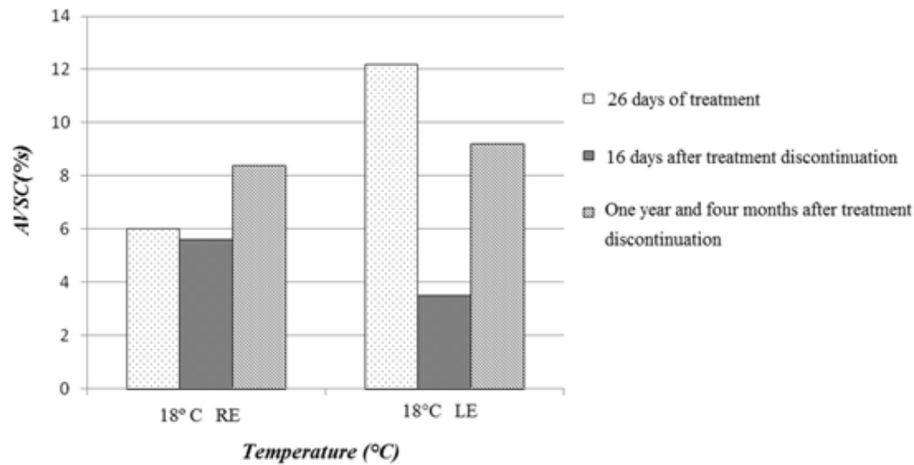
DISCUSSION

We reported the first well documented case on cochlear-vestibular toxicity related to MA diagnosed during a longitudinal study with patients with TL submitted to vestibular and auditory evaluation when under treatment with antimonials.

The patient had been using other drugs for a long term, without dizziness or tinnitus complaints, before beginning treatment with MA, thus we assumed that those drugs did not influence the development of such symptoms. This hypothesis is favored by the time factor, since the worsening of auditory thresholds, tinnitus and dizziness started



Graph 1 - Pure tone audiometry through air conduction of the left ear of a patient during monitoring - IPEC, FioCruz, Rio de Janeiro, 2011.



Graph 2 - Variations of Angular Velocity of the Slow Component of Nystagmus in degrees per second (AVSC °/s) of the patient during monitoring - IPEC, FioCruz, Rio de Janeiro, 2011. RE - Right Ear; LE - Left Ear.

after initiating MA treatment, following a reasonable time after drug administration, when the levels of this drug were well established in body fluids and tissues⁷, and it was confirmed because signs and symptoms improved when the treatment was discontinued, thus showing that a relationship between these adverse effects and MA is likely to be true. Although infection has not responded to treatment with MA, we do not believe that the outcome of the infection may have had an influence on the MA ototoxicity, since the disease itself would not be capable of causing the sensorineural changes found in this patient. The success of treatment with pentavalent antimonials depends on the peak value reached in serum or the maintenance of a minimum inhibitory concentration in serum, during most part of the time³. The finding that pentavalent antimonial is rapidly excreted in the urine, resulting in sub therapeutic serum levels in a few hours, led to the conclusion that the risk of cumulative toxicity is low and that intermittent therapeutic schemes are pharmacologically inconsistent^{3,7}. However, *in vivo* evidences of meglumine antimoniate conversion from Sb⁵⁺ into Sb³⁺ and the accumulation of Sb³⁺ in the tissues suggest that Sb³⁺ production could be responsible for the sustained activity of the drug, both therapeutic and toxic. Just a small conversion of the Sb⁵⁺ drug seems to occur during the phase of rapid excretion, however, it is followed by a phase of slow excretion of a high proportion of Sb³⁺ with a half-life of more than 50 days⁷. This pharmacokinetic behavior could explain the worsening of the auditory thresholds and AVSC at 18 °C alterations up to 28 days after discontinuing the treatment. Additionally, the patient had mucosal leishmaniasis which requires a treatment of 30 days with MA. Therefore, ototoxicity could not have been so intense, if he had cutaneous leishmaniasis which requires a shorter treatment time up to 21 days.

However, the use of other ototoxic drugs may lead to more frequent cochlear-vestibular toxicity which, in this particular case, could have been enhanced by the use of doxazosin mesylate and hydrochlorothiazide, both potentially ototoxic¹³. Non-steroidal anti-inflammatory drugs (NSAIDs) are related to reversible ototoxicity, with 1% to 3% incidence¹⁷. They can induce vestibular disorders, less frequent than auditory disorders, such as tinnitus and hearing loss. The effect is more metabolic than structural, usually reversible, and proportional to the plasma concentration of the toxic drug. However, the patient had been using this drug for the last

seventeen years, sporadically, without reporting any audio vestibular symptom^{5,14,17}.

Our study failed in not performing high frequency audiometry, since cochleotoxicity can occur, initially or solely, at the high frequency series from 9 to 20 kHz. Thus, the use of audiometry at conventional frequencies only, could have hindered an earlier and/or bilateral alteration in this case study¹. The role of effective monitoring of the cochlear function in early detection of ototoxicity of DPOAE has been reported, through drop of their responses¹⁸. In this patient, this assessment was hampered because the DPOAE were already absent at the beginning of treatment. However, the evolution of the reported case was documented through serial examinations¹⁶.

The occurrence of subclinical ototoxicity of some drugs¹ diagnosed by audiometry control has been described. To our knowledge, this is the first controlled case study of ototoxicity related to MA. This explains the fact that we could not find in literature references of hearing loss caused by this drug.

The most frequently reported adverse effects of pentavalent antimonials were musculoskeletal pain, gastrointestinal disturbances, mild to moderate headache, electrocardiographic QTc interval prolongation, mild to moderate increase in liver and pancreatic enzymes and significant suppression of mean lymphocyte and platelet counts^{11,19}. However, cochlear-vestibular toxicity is not frequently reported. Tinnitus and dizziness had already been reported during ML treatment with tartar emetic⁹. Considering a recent report stating that Sb³⁺ levels represent more than 30% of total Sb concentrations in Glucantime®, we can suppose that Glucantime® may not be so different from trivalent antimonial tartar emetic and that Sb³⁺ may account for its ototoxicity¹⁵. The patient studied in the present case was a senior, male, and presented renal, hepatic and pancreatic toxicity. Dizziness associated to the use of meglumine antimoniate has already been reported regarding females, aged 60 years or more and related to pancreatic toxicity². Because of its toxicity, meglumine antimoniate should be used with caution in patients older than 60 years⁸.

As for vestibular toxicity, the most common finding is hyporeflex or

simply normal reflex associated to vestibular complaints of the patient. Besides, it has been described that a reduction of 50% or more of the vestibular system, in at least one ear, indicates vestibular toxicity¹⁰. Although all the examinations of this case presented AVSC at 18 °C within normal reflex values, it is evident that a reduction of more than 50% of this value occurred from the beginning of symptoms to 16 days after treatment, and that, a year later, the patient being asymptomatic, there was a return to values similar to the beginning of symptoms. Unfortunately, we do not have values before treatment to compare. Apparently tinnitus and dizziness are not related, since time of maximum tinnitus alteration did not correspond to that of maximum dizziness.

At the end of the ongoing longitudinal study, we intend to clarify some aspects related to the ototoxicity of meglumine antimoniate, such as dose dependence, relation with treatment duration, reversibility or not, as well as the associated risk factors.

RESUMO

Primeiro relato de ototoxicidade pelo antimoniato de meglumina

Introdução: Antimoniais pentavalentes são os fármacos de primeira escolha no tratamento da leishmaniose tegumentar. Dados de ototoxicidade relacionados a tais fármacos são escassos na literatura, o que nos levou a desenvolver um estudo de funções cócleo-vestibulares. **Relato de caso:** Relatamos caso de paciente masculino de 78 anos com leishmaniose tegumentar, que apresentou aumento significativo dos limiars auditivos com zumbido e tontura rotatória grave durante o tratamento com antimoniato de meglumina. Os sintomas pioraram até duas semanas após a interrupção do tratamento. **Conclusão:** Tontura e zumbido já tinham sido associados ao antimoniato de meglumina. Entretanto, este é o primeiro caso bem documentado de toxicidade cócleo-vestibular relacionado ao antimoniato de meglumina.

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Cláudia Maria Valet-Rosalino has full access to all the data in the study and takes responsibility for their integrity.

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