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Main Article

Risk factors associated with dizziness during treatment of mucosal leishmaniasis with meglumine antimoniate: 16-year retrospective study of cases from Rio de Janeiro, Brazil

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Abstract

Objective: To evaluate dizziness in patients receiving meglumine antimoniate for the treatment of mucosal leishmaniasis.

Materials and methods: We retrospectively studied 127 patients treated at the Laboratory of Leishmaniasis Surveillance, Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, between 1 January 1989 and 31 December 2004.

Results: A low dose of meglumine antimoniate (5 mg/kg/day) was used in 86.6 per cent of patients; a dose of 10 mg/kg/day or higher was used in 13.4 per cent of patients. Dizziness was reported by 4.7 per cent of patients. The adjusted odds ratios were 7.37 for dizziness in female patients, 4.9 for dizziness in patients aged 60 years or older, and 7.77 for dizziness in the presence of elevated serum lipase.

Conclusion: We suggest that dizziness may be a side effect of meglumine antimoniate, particularly in elderly individuals, in females and in patients with elevated serum lipase.

Key words: Leishmaniasis; Meglumine Antimoniate; Dizziness; Ototoxicity

Introduction

Mucosal leishmaniasis is a form of American tegumentary leishmaniasis caused by the parasite *Leishmania (Viannia) braziliensis*.[1,2] In many cases, mucosal leishmaniasis results from the vascular dissemination of *L (Viannia) braziliensis* from skin lesions.[3]

Although therapeutic practice varies from country to country, leishmaniasis has been preferentially treated with antimonials for more than 60 years.[1,4] The two main therapeutic agents, meglumine antimoniate and sodium stibogluconate, differ in terms of dosage, treatment duration and administration frequency (continuous or intermittent).[5–9] At the Laboratory of Leishmaniasis Surveillance, Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, we have found continuous or intermittent intramuscular administration of meglumine antimoniate at a dose of 5 mg/kg/day to be effective and well tolerated.[10–15]

The main side effects of treatment with pentavalent antimonials are myalgia, arthralgia, electrocardiographic Q–T interval prolongation, renal failure and pancreatitis accompanied by elevated lipase levels, among others.[7,11,13,16,17] Older individuals are more affected by mucosal leishmaniasis and also more prone to the side effects of treatment,[13] in addition to presenting other risk factors for the occurrence of dizziness. In recent years, our group has occasionally observed dizziness in elderly patients, related to the use of meglumine antimoniate. Dizziness has been reported as an adverse effect of meglumine antimoniate used to treat American tegumentary leishmaniasis.[18] However, there are no published data describing possible risk factors associated with episodes of dizziness occurring during pentavalent antimonial treatment for mucosal leishmaniasis.

The term dizziness is used to describe a sensation of unsteadiness that manifests as instability, oscillation, fluctuation and deviation of gait, disequilibrium, fainting, short episodes of mental confusion, loss of consciousness, spatial disorientation, and epileptiform episodes. Dizziness should be distinguished from vertigo, which refers to the perceived movement of one's own body or of the environment, and is sometimes accompanied by nausea.[19,20] The risk

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factors associated with dizziness include cardiovascular, cerebrovascular, neurological, sensory, osteoarticular, psychological and gastrointestinal diseases, as well as diabetes.[13,20–29]

In Brazil, dizziness has attracted little public health interest, and its association with medication usage has not been well studied.[28] International studies suggest that a complete patient history and physical examination are more important for the diagnosis of dizziness than are complementary examinations.[23,30,31] Studies also suggest that predisposing factors may not have such a specific relationship with the aetiological diagnosis as has previously been thought.[25,27,29,32]

The aim of the current study was to determine the factors associated with the occurrence of dizziness in patients with mucosal leishmaniasis treated with meglumine antimoniate.

Materials and methods

We conducted a descriptive, retrospective study which reviewed the medical records of patients with mucosal leishmaniasis who had been treated with meglumine antimoniate at the Laboratory of Leishmaniasis Surveillance, Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil, between 1 January 1989 and 31 December 2004.

The criteria for the diagnosis of mucosal leishmaniasis were: a compatible epidemiological history; suggestive mucosal lesions as seen on video-nasopharyngolaryngoscopy; a positive Montenegro skin test and/or visualisation of the parasite on histopathological examination, imprint or culture; and (eventually) positive serology by indirect immunofluorescence or enzyme immunoassay.

Patients with other forms of American tegumentary leishmaniasis and those treated with drugs other than meglumine antimoniate were excluded.

Patients were treated with either (1) an intramuscular dose of 5 mg meglumine antimoniate/kg/day until epithelialisation of the lesion, no more than 120 doses, or (2) an intramuscular dose of ≤10 mg meglumine antimoniate/kg/day for 30 days. In both dosage groups, patients received the medication either continuously, or in an intermittent regime of 10 days with medication followed by 10 days without medication.

Clinical and laboratory examinations were conducted before, during, on completion and one month after completion of treatment to monitor toxicity. These included routine serum biochemical analyses (investigating serum glucose, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST) urea, creatinine, amylase and lipase), haematological examinations and electrocardiography.

Dizziness was considered as an adverse effect only if it appeared during treatment or up to one month after treatment completion. No specific tests, such as vestibular function tests, were available during the study period.

The analysed variables were selected because of their possible relevance to the onset and progression of dizziness in the group investigated (Tables I and II). The severity of clinical, biochemical, haematological and electrocardiographic side effects was classified according to an adapted version of the 1992 acquired immunodeficiency syndrome table for grading the severity of adult adverse experiences, in which G1 = mild side effect, G2 = moderate side effect, G3 = severe side effect and G4 = life-threatening side effect.[33]

TABLE I

CHARACTERISTICS OF CONTINUOUS PATIENT VARIABLES, BY PRESENCE OR ABSENCE OF DIZZINESS

Variable	Dizziness		p^*
	Present	Absent	
Age (y)	63.50 ± 19.52	49.59 ± 19.22	0.086
Total MA dose (n)	26.83 ± 7.76	41.98 ± 49.01	0.453
Treatment duration (d)	48.33 ± 27.14	47.41 ± 26.78	0.934

Data represent means ± standard deviations unless otherwise specified. *Significant at 20 per cent level. Y = years; MA = meglumine antimoniate

Categorical variables (i.e. gender, treatment type and occurrence of adverse events) were reported as simple frequencies. Measures of central tendency and dispersion were used for discrete or continuous quantitative variables (i.e. age, duration of treatment and total dose). The strength of the association between dizziness and the covariables of interest was evaluated using odds ratios and 80 per cent confidence intervals. Significant differences between the proportions were determined using Fisher's exact test, and the differences between the means of continuous variables were evaluated using Student's *t*-test. Variables were selected according to their theoretical relevance or statistical significance (considered at $p < 0.20$), and were analysed by a stepwise (backward elimination using Wald's test), non-conditional logistic regression. The entry criterion was set at 0.10 ($p < 0.10$) and the retention criterion at 0.15 ($p > 0.15$), for the Wald statistical test. The Hosmer–Lemeshow test showed no lack of fit ($p > 0.05$). The data were processed and analysed using the Statistical Package for the Social Sciences software package (version 11.0).

The project was approved by the ethics committee on research involving humans of the Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation.

Results and analysis

We studied a total of 127 patients (31.4 per cent females, 68.6 per cent males) ranging in age from four to 90 years (mean ± standard deviation (SD), 50.9 ± 19.4 years). Of these patients, 110 (86.6 per cent) were treated with 5 mg meglumine antimoniate/kg/day and 17 (13.4 per cent) with ≥10 mg meglumine antimoniate/kg/day. The continuous and intermittent regimens were used in 71.8 and 28.2 per cent of patients receiving 5 mg meglumine antimoniate/kg/day, respectively, and in 82.35 and 17.64 per cent of patients receiving ≥10 mg

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TABLE II

DISTRIBUTION OF PATIENT VARIABLES* BY PRESENCE OR ABSENCE OF DIZZINESS

Variable	Dizziness?				OR	p**
	Yes†		No‡			
	n	%	*n*	%		
Female gender	38	30.2	4	66.7	4.63	0.081
CV side effects	1	0.8	1	16.7	23.80	0.093
↑ Serum creatinine	22	18.3	1	16.7	0.89	1.000
↑ Serum lipase	10	8.3	2	33.3	5.50	0.101
↑ Serum urea	15	12.6	1	16.7	1.40	0.565
Hyperglycaemia	8	6.7	1	16.7	2.80	0.365
↑ Serum AST	15	12.6	1	16.7	1.40	0.565
↑ Serum ALT	9	7.6	1	16.7	2.47	0.398
Hypercholesterolaemia	4	3.4	1	16.7	5.80	0.220
ECG changes	20	16.7	1	16.7	1.00	1.00
Age ≥60 years	45	35.7	4	66.7	3.60	0.194
MA dose >5 mg/kg/day	16	13.2	1	16.7	1.31	0.586

*Monitored before, during and ≥30 days after completion of meglumine antimoniate (MA) treatment. †$n = 121$; ‡$n = 6$. **Significant at 20 per cent level. OR = odds ratio; CV = cardiovascular; ↑ = raised; AST = aspartate transaminase; ALT = alanine transaminase; ECG = electrocardiograph

meglumine antimoniate/kg/day, respectively. The duration of treatment ranged from 4 to 133 days (mean ± SD, 47.4 ± 26.7 days), with 115 (90.5 per cent) patients completing treatment. Twelve (9.5 per cent) patients did not complete treatment: six due to drop-out, five due to the presence of side effects, and one due to other, non-specified reasons. Therapeutic success was obtained in 102 (88.6 per cent) of the 115 patients who completed the treatment.

Dizziness was reported by 4.7 per cent of the 127 patients. When comparing the means of continuous variables, only patient age showed a statistically significant association with dizziness ($p < 0.086$) (Table I).

A bivariate analysis at a level of significance of 20 per cent showed significant associations between dizziness and female gender, patient age of 60 years or older, elevated serum lipase and the presence of cardiovascular alterations (Table II). The other variables cited in Table II were included in the logistic regression model due to their theoretical relevance.

Table III shows the crude and logistic regression adjusted odds ratios for the occurrence of dizziness in the presence of various categorical variables, together with 90 per cent confidence intervals. These results show that only female gender, age of 60 years or older and elevated serum lipase remained significant.

Discussion

Although leishmaniasis is an important endemic disease and a public health issue in underdeveloped countries, the increase in developing world tourism has resulted in the extension of this problem to developed countries.[34]

As our study was retrospective, the validity of our data could be questioned due to the lack of objective testing of outcome measures (e.g. by vestibular tests) and the lack of detailed history-taking regarding the nature of the dizziness. Dizziness is a subjective symptom which represents different and overlapping sensations, and which may be caused by different pathophysiological mechanisms representing several differing diagnoses.

On the other hand, the strong points of our study included regular patient follow up, and systematic investigation of side effects by clinical, biochemical, haematological and electrocardiographic examination, thus permitting evaluation of a large number of variables.

Ototoxicity is a relatively rare cause of disequilibrium which is related to the use of chemical substances. There are a wide variety of ototoxic drugs (at least 130), the most commonly used being aminoglycoside antibiotics, salicylates, quinine, antineoplastic agents and loop diuretics. Risk factors associated with ototoxicity include an elevated concentration of the drug in serum or in the inner ear, hypoalbuminaemia, renal function impairment, previous inner ear damage, previous or concomitant treatment with another ototoxic medication, fever, dehydration, bacteraemia, hereditary factors, female gender, noise exposure, and advanced age.[35] In the present study, a

TABLE III

CRUDE AND ADJUSTED* ODDS RATIOS AND CONFIDENCE INTERVALS FOR OCCURRENCE OF DIZZINESS IN THE PRESENCE OF VARIOUS CATEGORICAL VARIABLES

Variable	Cr OR	p	Adj OR	p†	CI
Gender					
– Female	4.63	0.081	7.37	0.042	1.47–36.99
– Male	1.00		1.00		
↑ Serum lipase					
– Present	5.50	0.101	7.77	0.048	1.41–42.88
– Absent	1.00		1.00		
Age (y)					
– ≥60	3.60	0.194	4.90	0.096	1.02–23.48
– <60	1.00		1.00		

*By logistic regression. †Significant at 10 per cent level. Cr = crude; OR = odds ratio; adj = adjusted; CI = confidence interval; y = years

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higher risk of dizziness was observed among females, elderly individuals and those with elevated serum lipase.

We found no association between dizziness and treatment duration, a drug dose of ≥10 mg meglumine antimoniate, or receiving a greater number of meglumine antimoniate doses. This is probably because most patients received the low-dose regimen (5 mg meglumine antimoniate/kg/day) usually used in our service.

The most common cardiovascular side effects associated with the use of meglumine antimoniate are electrocardiographic Q–T interval prolongation and arrhythmias.[7,11,12] However, no significant association has been observed between dizziness and alterations in cardiac rhythm.[21] Similarly, in the present study multivariate logistic regression analysis revealed no association between dizziness and cardiovascular side effects.

The association between dizziness and diabetes is controversial, and has been reported by some investigators[20,21,27] but not others.[22–24,36] We found no association between hyperglycaemia and dizziness.

- **Meglumine antimoniate is used to treat mucosal leishmaniasis**
- **Dizziness may be an adverse effect of this drug, especially in females, elderly individuals and those with elevated serum lipase**
- **If meglumine antimoniate treatment is not interrupted, permanent vestibular damage may occur**

The data reported here suggest that there is no association between dizziness and altered renal function (as detected by conventional laboratory analysis). This conclusion is in contrast with published literature which suggests that nephrotoxic drugs may be potentially ototoxic, whereas the use of substances with a known nephroprotective action may be potentially otoprotective.[37–39] Analysis of other biochemical parameters indicated no association between dizziness and hypercholesterolaemia or hepatic alterations; this is in agreement with the literature.[19,30,40]

Previous studies have reported an association between gastrointestinal medication usage and dizziness,[41] as well as between gastrointestinal disease and dizziness.[28] Our findings agree with these reports, and show that elevated serum lipase levels, indicating pancreatic toxicity related to the use of meglumine antimoniate, are an important risk factor for the development of dizziness among patients taking this drug.

Conclusions

These study findings indicate that dizziness may occur as an adverse effect related to the use of meglumine antimoniate, especially in females, elderly individuals and those with elevated serum lipase. If meglumine antimoniate treatment is not interrupted, permanent vestibular damage may occur.

As a result of these observations, we are conducting additional studies with complete cochleo-vestibular evaluation, to better investigate meglumine antimoniate related ototoxicity.

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