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ORIGINAL ARTICLE

PANCREATIC TOXICITY AS AN ADVERSE EFFECT INDUCED BY MEGLUMINE ANTIMONIATE THERAPY IN A CLINICAL TRIAL FOR CUTANEOUS LEISHMANIASIS

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SUMMARY

American tegumentary leishmaniasis is an infectious disease caused by a protozoan of the genus *Leishmania*. Pentavalent antimonials are the first choice drugs for cutaneous leishmaniasis (CL), although doses are controversial. In a clinical trial for CL we investigated the occurrence of pancreatic toxicity with different schedules of treatment with meglumine antimoniate (MA). Seventy-two patients were allocated in two different therapeutic groups: 20 or 5 mg of pentavalent antimony (Sb^{5+})/kg/day for 20 or 30 days, respectively. Looking for adverse effects, patients were asked about abdominal pain, nausea, vomiting or anorexia in each medical visit. We performed physical examinations and collected blood to evaluate serum amylase and lipase in the pre-treatment period, and every 10 days during treatment and one month post-treatment. Hyperlipasemia occurred in 54.8% and hyperamylasemia in 19.4% patients. Patients treated with MA 20 mg Sb^{5+} presented a higher risk of hyperlipasemia ($p = 0.023$). Besides, higher MA doses were associated with a 2.05 higher risk ratio ($p = 0.003$) of developing more serious (moderate to severe) hyperlipasemia. The attributable fraction was 51% in this group. Thirty-six patients presented abdominal pain, nausea, vomiting or anorexia but only 47.2% of those had hyperlipasemia and/ or hyperamylasemia. These findings suggest the importance of the search for less toxic therapeutic regimens for the treatment of CL.

KEYWORDS: Cutaneous leishmaniasis; Therapy; Clinical trial; Meglumine antimoniate; Pancreatitis.

INTRODUCTION

Leishmaniasis is endemic in Brazil and in other countries worldwide with an estimated incidence of one million cases each year[1]. In *Rio de Janeiro*, almost all the cases of American Tegumentary Leishmaniasis (ATL) are caused by *Leishmania braziliensis*[2]. The possibility of infection depends on sandfly density, sources of infection for these vectors, and the existence of susceptible human and animal populations[3].

Sodium stibogluconate and meglumine antimoniate (MA) are pentavalent antimony (Sb^{5+}) derivatives used in the treatment of ATL and they are considered similar in terms of efficacy and toxicity. Regular treatment with pentavalent antimonials (10-20 mg Sb^{5+}/kg/day) may result in several adverse effects such as arthralgia, myalgia, transient elevation of hepatocellular enzyme levels, and electrocardiogram (ECG) changes. Other more severe adverse events include acute renal failure, leucopenia and pancreatitis, sometimes leading to the permanent discontinuation of the treatment with these drugs. In this context, a less toxic alternative schedule with MA 5 mg Sb^{5+}/kg/day[4,5] have demonstrated to be particularly useful in older patients and in those with co-morbidities[6].

Bradley *et al.*[7] defined acute pancreatitis (AP) as an acute inflammatory

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process of the pancreas with variable involvement of regional tissues or remote organ systems, associated with raised pancreatic enzymes levels in blood and/or urine; AP can vary from asymptomatic laboratory abnormalities (hyperamylasemia and/ or hyperlipasemia) to severe clinical manifestations or death. Other authors[8] defined an AP diagnosis as the presence of two or more of the following characteristics: abdominal pain, typical imaging features as found on tomography or magnetic resonance imaging, or at least a threefold increase of serum amylase and/ or lipase levels, above the upper normal limit. However, there is no agreement regarding the exact serum amylase or lipase levels required for a diagnosis of AP[9].

Drug-induced pancreatitis has been described[10] and represents 2- 5% of reported cases of AP in the general population[8,11]. After the initial reports proposing an association between acute pancreatitis and antimonial therapy[12], it has been suggested that nausea, vomiting and abdominal pain, that have been long recognized adverse effects of the antimonial compound, could be related to pancreatic disorders[13].

Although pancreatic toxicity (PT) have also been described in ATL[13] almost all the AP cases associated with the use of pentavalent antimonials have been initially reported in adults with visceral leishmaniasis[14], and most of them were also renal transplant recipients[15] or were co-infected with HIV[16]. Most of these patients had received other drugs potentially toxic to the pancreas in combination with antimony, a fact that has probably increased the toxicity[12,17]. However, some of the patients who developed pancreatitis were not taking potentially toxic drugs, were not alcoholics, had normal triglyceride levels, and their biliary tract was normal according to the abdominal ultrasound examination[18-20].

Some questions are still unanswered: what is the real frequency of PT related to antimonial therapy? Is there any correlation of PT with the dose of pentavalent antimonial? We therefore investigated PT in 72 patients treated with 20 or 5 mg Sb^{5+}/kg/day of MA included in a clinical trial for cutaneous leishmaniasis (CL).

MATERIALS AND METHODS

Patients with CL have been enrolled in a controlled, randomized, blinded, phase III clinical trial of equivalence among the standard treatment regimens and alternative ones with MA (Glucantime ® - Aventis-Pharma - *São Paulo*, batch number 604898) administered intramuscularly. The drugs were provided by the National Health Ministry. The trial was registered on ClinicalTrials.gov - Identifier: NCT01301924. Blinding was maintained during data analysis. The study was performed at the Leishmaniasis Surveillance Laboratory (VIGILEISH), *Evandro Chagas* National Institute of Infectious Diseases (INI), *Oswaldo Cruz* Foundation (FIOCRUZ), Brazil, between 2008 and 2012. Patients with CL, over 12 years old, infected in *Rio de Janeiro*, presenting positive results for *Leishmania* through one or more methods (scraping technique, histopathology, culture, immunohistochemistry and polymerase chain reaction – PCR) and absence of previous treatment with MA were included. Exclusion criteria were: pregnant women, patients on immunosuppressive therapy, presence of clinical signs/symptoms that are equivalent to adverse effects (AE) level ≥ grade 3 or laboratory abnormalities equivalent to AE level ≥ grade 2. The severity of AE (clinical and laboratory) was adapted from "AIDS Table for Grading Severity of Adult Adverse Experiences, 1992"[21] (Table 1).

Seventy-two enrolled patients, after signing an informed consent, were randomly assigned to one of the two treatment groups: Group A - 20mg Sb^{5+}/kg/day for 20 days, Group B – 5 mg Sb^{5+}/kg/day for 30 days. The maximum daily dose of antimony did not exceed 1,215 mg Sb^{5+}/kg, as recommended by the Brazilian Health Ministry[2]. Patients were randomized in blocks of 12, with six patients distributed in each group, amounting to 36 per group. Data from all included patients were analyzed according to intention to treat.

Patients were asked about abdominal pain, nausea, vomiting or anorexia and underwent physical examination with abdominal palpation and evaluation of serum amylase and lipase in pre-treatment, every 10 days during treatment and one month after completion of treatment. Considering the reference levels, we defined PT as any level of increased serum lipase or amylase[21].

Clinical AE were evaluated by a single researcher according to a standard form to collect data. We only evaluated data of AE as related to MA when they were considered as definitive or probably related to the drug, defined as: 1) Definitive - relationship with temporal introduction or discontinuation of MA followed by a known response of the suspected

Table 1
Degrees of clinical toxicity and laboratory abnormalities adapted from "AIDS Table for Grading Severity of Adult Adverse Experiences, 1992"

	Toxicity degree			
	Grade 1 - mild	Grade 2 - moderate	Grade 3 - severe	Grade 4 - potentially life threatening
Signs and symptoms	Sign or symptom transient or mild without activity limitation, without need for medical care or treatment	Activity limitation mild to moderate, may require medical care or treatment	Important activity limitation, need for medical care or treatment, possible hospitalization	Extreme activity limitation, great need for medical care and treatment and probable hospitalization
Amylase	> 1.0 - 1.5 x ULN*	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN
Lipase	> 1.0 - 1.5 x ULN	> 1.5 - 2.0 x ULN	> 2.0 - 5.0 x ULN	> 5.0 x ULN

Methodology for lipase: colorimetric / bichromatic; Kit Lipase reference DF55A; methodology for amylase: enzymatic/ chromatic, Kit Amylase reference DF27; manufactured by SIEMENS HEALTHCARE DIAGNOSTICS LTD. NEWARK, DE 19714 U.S.A; Reference levels in INI laboratory: amylase 25 - 115 U/L; lipase 73 - 287U/L (*ULN = Upper Limit of Normal Reference Level)

drug; 2) Probable - relationship with temporal introduction of MA followed by a known drug response, which could have been produced by other unrelated event.

The statistical analysis was performed using SPSS version 19.0 (IBM Corp, Armonk, NY, USA), Stata version 12.0 (Stata Corp, College Station, TX, USA) and StatXact-8 (Cytel Inc, Cambridge, MA, USA). The chi-square test was used to perform comparisons of categorical variables; *p*-values < 0.05 indicated significant associations.

RESULTS

Among the 72 studied patients, the mean age was 39 years (SD±16.7), ranging from 15 to 71 years; males have predominated (69.4%). The patients' distribution among treatment groups was homogeneous regarding gender, age and educational level. Fifty percent presented some gastrointestinal manifestation compatible with pancreatitis: anorexia (33.3%), nausea (29.1%), vomiting (15.3%) and abdominal pain (18.0%). Among 36 patients with gastrointestinal complaints, 47.2% had increased serum lipase or amylase. The most frequent reported symptoms (88.4%) were considered mild, while 11.6% had moderate intensity. The frequency of these symptoms was higher in group A than in group B, although not statistically significant.

Hyperamylasemia was present in 14 (19.4%) patients: 13 with grade I and one with grade II. Hyperamylasemia was always accompanied by hyperlipasemia, however it was not significantly associated with any of the studied variables: age, gender, high or low doses. We were unable to perform serum lipase dosage in 10 patients (4 in the high and 6 in the low dose groups). Among the 62 patients that underwent lipase dosage, 34 (54.8%) patients had hyperlipasemia: 17 grade I, 10 grade II and 7 grade III (Table 2). According to the security protocols of the study, 7 patients with grade III hyperlipasemia had to temporarily discontinue the treatment, among them one patient received treatment with 5mg Sb^{5+}/kg/day and six patients with 20 mg Sb^{5+}/kg/day. One of these last six patients died.

Elevated serum lipase was frequent in both treatment groups 20 mg Sb^{5+}/kg/day (68.8%) and 5 mg Sb^{5+}/kg/day (40.0%). The group who received 20 mg Sb^{5+}/kg/day showed a more frequent increase of serum lipase (RR = 1.81) (p = 0.023). There were no associations between the presence of hyperlipasemia and gender or age (> 50 years), as shown in Table 3.

We found a significant association between high dose and intense hyperlipasemia, with grade II or III (moderate/severe) being more frequent in patients treated with 20 compared to 5 mg Sb^{5+}/kg/day of MA (p = 0.003). The attributable fraction (AF) was 51% for higher doses. Other variables as age and gender were not significantly associated with hyperlipasemia severity (Table 4).

Table 2
Adverse effects according to intensity and group of treatment

Adverse effect		Group of Treatment		Total n (%)
		20mg Sb^{5+}/kg/day N (%)	5 mg Sb^{5+}/kg/day n (%)	
Hyperlipasemia* (N=62)	Grade I	08 (12.9)	09 (14.5)	17 (27.4)
	Grade II	08 (12.9)	02 (3.2)	10 (16.1)
	Grade III	06 (9.7)	01** (1.6)	07 (11.3)
	Total	22 (35.5)	12 (19.3)	34 (54.8)
Hyperamylasemia (N=72)	Grade I	09 (12.5)	04 (5.6)	13 (18.1)
	Grade II	01 (1.4)	0	01 (1.4)
	Total	10 (13.9)	04 (5.5)	14 (19.4)
Hyperlipasemia + Hyperamylasemia* (N=62)**		10 (13.9)	03 (4.2)	13 (18.1)
Anorexia (N=72)	Grade I	17 (23.6)	07 (9.7)	24 (33.3)
Vomiting (N=72)	Grade I	05 (6.9)	05 (6.9)	10 (13.9)
	Grade II	01 (1.4)	0	01 (1.4)
Abdominal pain (N=72)	Grade I	06 (8.3)	02 (2.8)	08 (11.1)
	Grade II	02 (2.8)	03 (4.1)	05 (6.9)
Náusea (N=72)	Grade I	08 (11.1)	11 (15.2)	19 (26.3)
	Grade II	01 (1.4)	01 (1.4)	02 (2.8)

N = Total number of evaluated patients; n = Number of patients with altered exam or symptom. % = percent of patients with altered exam or symptom. * Only 62 patients had serum lipase measured, 30 in 5 mg/kg/day group and 32 in 20 mg/kg/day group. ** Patient was included in the study with hyperlipasemia grade I. *** One patient with hyperamylasemia had not serum lipase measured; Sb^{5+} = pentavalent antimony

Table 3
Association between hyperlipasemia and therapeutic schedules with meglumine antimoniate (MA) for the treatment of cutaneous leishmaniasis (CL), according to age and gender

Variable		Hyperlipasemia n/N (%)	RR	95%CI	RD	AF(%)	*p-value*
Therapeutic scheme	20mg Sb^{5+}/kg/day	22/32 (68.8)	1.81	1.04 – 3.16	0.29	45%	0.023
	5mg Sb^{5}/kg/day	12/30 (40.0)	1				
Age	≥ 50	11/20 (55.0)	1.01	0.49 - 2.08	0.00	0.6%	NS
	15 – 49	23/42 (54.8)	1				
Gender	Male	23/42 (54.8)	0.99	0.71 - 1.41	0.00	0.3%	NS
	Female	11/20 (55.0)	1				

N = Total number of evaluated patients. n = Number of patients with hyperlipasemia. % = percent of patients with hyperlipasemia. NS = not significant. RR = Risk Ratio. 95% CI = 95% Confidence Intervals. RD = Risk Difference. AF = Attributable Fraction.

Table 4
Association between moderate and severe degrees of hyperlipasemia and therapeutic schedules with meglumine antimoniate (MA) for the treatment of cutaneous leishmaniasis (CL), according to age and gender

Variable		Hyperlipasemia* Grades II or III n/N (%)	RR	95% CI	RD	AF	*p valor*
Therapeutic scheme	20 mg Sb^{5+}/kg/day	14/32 (43.8)	2.05**	1.35 - 3.13	0.42	51%	0.003
	5 mg Sb^{5}/kg/day	3/30 (10.0)	1				
Age	≥ 50	6/20 (30.0)	1.13	0.52 - 2.46	0.04	11%	NS
	15 – 49	11/42 (26.2)	1				
Gender	Male	11/42 (26.2)	0.94	0.63 - 1.40	- 0.04	06%	NS
	Female	6/20 (30.0)	1				

N = Total number of evaluated patients. n = Number of patients with hyperlipasemia. % = percent of patients with hyperlipasemia. *Grade II: moderate and grade III: Severe. NS = not significant. RR = Risk Ratio. 95% CI = 95% Confidence Intervals. RD = Risk Difference. AF = Attributable Fraction.

DISCUSSION

In this trial, we observed PT associated with the use of MA in 54.8% of the studied patients with CL, suggesting that this adverse effect is more frequent than usually reported[22]. Several studies have associated PT with the use of pentavalent antimonials in the treatment of leishmaniasis, however most of them are case reports series or uncontrolled studies[23].

Increased serum lipase was the most common and the most severe laboratory abnormality, although hyperamylasemia was not significantly associated with any of the studied variables. Other authors agree that serum lipase is more sensitive and specific than serum amylase as a marker of early pancreatic toxicity[9,24]. In the presence of AP, serum lipase levels rise earlier and remain elevated for longer than serum amylase[25]. Despite this obvious advantage, the high cost of measurement of serum lipase has limited its routine use.

Patients treated with 20 mg Sb^{5+}/kg/day of MA presented a higher risk of developing hyperlipasemia than patients treated with 5 mg Sb^{5+}/kg/day. When evaluating only those patients with increased serum lipase levels grade II or III (moderate or severe), patients who received 20 mg Sb^{5+}/kg/day had even a higher risk of this adverse event. The fact that six out of the 7 patients who discontinued treatment due to grade III increased serum lipase had been treated with 20 mg Sb^{5+}/kg/day reinforces this hypothesis.

Gastrointestinal manifestations associated with antimonial treatment were reported[18,26]. Although in the present study half of the patients complained of gastrointestinal symptoms, we did not find an statistical association with hyperlipasemia/hyperamylasemia. Gasser *et al.*, studying different forms of leishmaniasis treated with sodium stibogluconate 20 mg Sb^{5+}/kg/day demonstrated that 98% of the patients with chemical pancreatitis had also hyperamylasemia and/ or hyperlipasemia, and 47% of them were symptomatic[13]. Similarly, Lawn *et al.*[23] found hiperamylasemia with sodium stibogluconate in 67% of ATL patients and a threefold amylase increase in 19% of the patients. However, the mechanism of pancreatic disorders during administration of MA or sodium stibogluconate for the treatment of leishmaniasis has not been well established[13].

One patient treated with 20 mg Sb^{5+}/kg/day died due to bacterial sepsis in another hospital, during a treatment interruption due to

hyperamylasemia grade II and hyperlipasemia grade III. Although data retrieved from her medical records failed to attribute the cause of death to pancreatitis, this relationship cannot be completely discarded. In all other six cases that had to interrupt treatment, normalization of serum amylase and lipase occurred during the period of interruption or at the end of treatment.

It is possible that only the most severe cases of pancreatitis with clinical complaints are routinely diagnosed in primary health care units. The use of schedules with 5 mg Sb^{5+}/kg/day, with lower pancreatic toxicity, may represent an advantage in developing countries where the dosage of amylase and lipase is not largely available in primary health care units. In Brazil, about 22,000 ATL patients are annually treated with 10 to 20 mg Sb5+/kg/day and around 90 deaths are recorded each year during treatment with MA[27]. It is possible that several of these deaths are related to drug toxicity and some of them could be due to pancreatitis induced by MA. Regarding efficacy, there was no statistically significant difference between treatment groups. This emphasizes the importance of the search for less toxic alternative therapeutic regimens for the treatment of CL in developing countries.

One of the strengths of the study results is the design of study, a randomized blinded clinical trial, conducted by trained personal, applying good clinical practice, using standardized instruments to collect data. Although the sample size was restricted to perform the univariate analysis, a significant difference among the studied groups was found.

Although the increase in serum amylase and lipase are referred to have good accuracy for the diagnosis of AP[9], some authors suggest the inclusion of clinical parameters and imaging results to define AP diagnosis[8]. Subsequent studies with implementation of imaging methods such as computerized tomography and magnetic resonance imaging would allow a better understanding of pancreatitis/ pancreatic toxicity induced by MA in patients with ATL.

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AUTHOR CONTRIBUTIONS

Marcelo R Lyra conceived and designed the experiments, performed the clinical examinations and wrote the paper; Sonia R L Passos conceived and designed the experiments and analyzed data; Maria I F Pimentel performed the clinical examinations, performed critical revision and final approval of article; Sandro J Bedoya-Pacheco analyzed data; Cláudia M Valete-Rosalino performed the clinical examinations; Erica C F Vasconcellos performed the clinical examinations; Liliane F Antonio performed the clinical examinations and analyzed data; Mauricio N Saheki performed the clinical examinations, analyzed data and wrote the paper; Mariza M Salgueiro performed the clinical examinations; Ginelza P L Santos performed the clinical examinations; Madelon N Ribeiro performed the clinical examinations; Fatima Conceição-Silva performed laboratory exams; Maria F Madeira performed laboratory exams; Jorge L N Silva performed laboratory exams; Aline Fagundes performed laboratory exams; Armando O Schubach conceived and designed the experiments, performed critical revision and final approval of article.

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COMPETING INTERESTS

The authors declare they have no competing interests.

ETHICAL APPROVAL

The trial was approved by the Research Ethics Committee of *Evandro Chagas* National Institute of Infectious Disease (INI), *Oswaldo Cruz* Foundation (FIOCRUZ), *Rio de Janeiro*, Brazil, under the number 0055.0.0009.000-07. It was registered on http://clinicaltrials.gov - Identifier: NCT01301924.

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