SAS Journal of Medicine (SASJM) **ISSN 2454-5112**
Abbreviated Key Title: SAS J. Med.

A Unit of Scholars Academic and Scientific Society, India

Side Effects of Systemic Treatment of Cutaneous Leishmaniasis by Glucantime®: Moroccan Experience

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Original Research Article

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Article History
Received: 17.12.2018
Accepted: 26.12.2018
Published: 30.12.2018

DOI:
10.21276/sasjm.2018.4.12.5

Abstract: Glucantime® is the standard treatment for cutaneous leishmaniasis in Morocco. The purpose of our study was to specify the adverse effects of systemic Glucantim, prescribed for cutaneous leishmaniasis. This is a retrospective study, conducted within the Department of Dermatology of the University Hospital Mohamed VI Marrakesh - Morocco over a period of 13 years, from January 2003 to June 2016. All hospitalized cases for cutaneous leishmaniasis were included and treated by Glucantime® at the dose of 20mg / kg / day for 10 to 15 days intramuscularly. The side effects of Glucantime®, a type of stibo-intolerance accident, occurred in 8 patients, 21% of Glucantime intramuscular treatments. The predominant skin reactions were inflammatory erythematous placards (37.5%), generalized pruriginous skin rash (12.5%) and arthro-myalgia (12.5%). The time of onset of these adverse effects varies from 1 to 14 days after the start of treatment. No cases of renal failure or cardiac disorders have been reported. In our series, we did not notice any serious side effects; however, the occurrence of these is possible and urges us to institute strict surveillance especially in elderly and fussy subjects.
Keywords: Cutaneous leishmaniasis, Glucantime®, adverses effects, Moroccan experience.

INTRODUCTION

Cutaneous leishmaniasis (CL) is a public health problem in Morocco; it is a parasitosis due to a flagellated protozoan belonging to the genus Leishmania, described for the first time in Morocco in 1914 by Foley and Vialate [1].

For more than 50 years, Glucantime has been the standard of treatment for the majority of cutaneous leishmaniases (CL). However, administered by the general route, it exposes many side effects of variable severity and whose frequency varies from 16 to 59% [2, 3].

The purpose of our work is to study the adverse effects of systemic Glucantim prescribed for cutaneous leishmaniasis.

METHODS

This retrospective study was conducted in the Department of Dermatology of the Mohamed VI University Medical Center Marrakech - Morocco over a period of 13 years, from January 2003 to June 2016. All hospitalized cases for cutaneous leishmaniasis were included and treated with Glucantime® at a dose of 20mg / kg / day for 10-15 days intramuscularly. The included cases had cutaneous leishmaniasis confirmed by dermal smear, histological examination. The use of the polymerase chain reaction (PCR) was made in two cases, the first being cutaneous leishmaniasis associated with visceral involvement and the second with leishmaniasis of the mucosa. Patient-specific variables were collected including age, antecedents, adverse effects of Glucantime®, and time to onset of treatment. In addition, these patients benefited from a pre-therapeutic assessment and a close medical supervision during the administration of the treatment. The pre-treatment assessment included blood count (NFS), lipasemia, amylasemia, renal and hepatic function, serum potassium, and electrocardiogram (ECG). The collected data has been entered and processed by the SPSS version 10 software.

RESULTS

The sample studied, with a total of forty-four patients, 30 women (68.2%) and 14 men (31.2%), showing a clear predominance of women. During the study period, of the 44 cases of leishmaniasis treated with systemic Glucantime®, 8 of them had side effects. According to the results of Table 1, the side effects of Glucantime® as a result of stibo-intolerance accidents occurred in 8 patients, but no case of stibio-intoxication was noted.

4.3).± The cutaneous reactions predominated and were represented by erythematous inflammatory placards (3 cases), or 37.5%, and a generalized pruriginous skin rash (1 case) followed by febrile peaks ranging from 38.5 ° C and 40 ° C noted in 3 patients apart from any infectious process, a transient elevation of transaminase levels was noted in one patient, arthro-myalgia was noted in 12.5%. However, these adverse effects decreased after stopping treatment. It should be noted that no cases of renal insufficiency or cardiac disorders have been reported. The time to onset of adverse reactions varies from 1 to 14 days after the start of treatment. For 2 cases they occurred during the first day, 4 cases during the first week (between 2 and 7 days), 1 case during the 2nd week (9th day) and 1 case on the 14th day after the beginning treatment. Thus, the average time to onset of these adverse effects is 7 days (6.5).

Table-1: Summary table of patients with parenteral glucantime® adverse reactions

	Age (years)	Sex	Antecedents	Time limit	Side effects
1	65	W	HTA, DT2	D2	Erythematous closets at the injection site
2	32	W	-	D1	Fever
3	58	W	-	D9	Arthro-myalgia
4	46	M	Smoking-chr.	D4	Fever & Erythematous closets at the injection site
5	59	W	DT2	D5	Skin rash
6	41	M	-	D14	Cytolyse (2 times normal)
7	37	W	-	D3	Erythematous closets at the injection site
8	29	W	-	D1	Fever

W: Woman, M: Man, DT2: diabetes Type 2, Smoking-chr. : Chronic Smoking, HTA: D: day

DISCUSSION

In Morocco, cutaneous leishmaniasis is still endemic and epidemic and its reference treatment remains Glucantime®, which is in the form of a 5 ml ampoule corresponding to 1.5g of meglumine antimony, 425 mg of pentavalent antimony.

The first pentavalent derivatives of antimony, Pentostam (sodium stibiogluconate) and Glucantime® (N-methylglucamine antimoniate) were synthesized in Germany in 1920 by Schmidt; their commercialization was carried out respectively in 1937 and 1946[4].

The dose of Glucantime® intramuscular prescribed to our patients was consistent with the doses proposed by the World Health Organization (WHO) and some publications that recommend doses of 15 to 20 mg / kg / day pentavalent antimony which corresponds to 60 mg / Kg / day of Glucantime ® [5].

This treatment regimen is indicated in patients with more than 5 lesions, or with a lesion greater than 4 cm in diameter, or sitting near a periorific or cartilaginous area.

The tolerance of this molecule is variable from one subject to another. Commonly, two tables of Glucantime® intoxication are described: stibiointolerance and stibiointoxication. Early onset and independent of an overdose, the first is manifested by signs of thermal shift, arthralgia, vomiting, quintessential cough and isolated or associated skin rashes, while the second is commonly end of treatment, or even after stopping it. Signs of intoxication include cardiac, hepatic, renal, pancreatic and hematologic involvement, but the severity of the side effects appears to be related to the total dose administered[6].

The prevalence of adverse effects of Glucantime® in our series is 18.2% of cases; prevalence lower than those found in many series; 24%, 21% and 33%[7-9]. However, this prevalence found in our series is within the frequency range of adverse events found in many series ranging from 16.3% to 59 % [2, 3]. As for the average time to onset of adverse effects in our sample, the value found (around the 7th day) is relatively similar to that revealed in the study by Masmoudi *et al*. [8] and is on the 8th day.

The cases of stibio-intolerance were noted in 8 patients with a clear predominance of cutaneous manifestations objectified in 4 patients. A skin rash was noted in one patient and three others had an urticarial reaction at the site of the injection. The high frequency of these cutaneous reactions has been explained by some authors, by the presence of impure heavy metals in the product [10]. Fever was observed in 3 patients. This frequency is consistent with that reported in the literature (15% to 22%). Arthralgia was noted in 12.5% of cases. These are the most common subjective side effects of Glucantime®[6].

In our series, no case of stibio-intoxication was noted, this can be explained by the small size of our sample or by the systematic realization of a pre-glucantime® balance in all our patients including: a numeration formula Blood (NFS), Lipasemia, amylasemia, renal and hepatic function, serum potassium and electrocardiogram (ECG), which made it possible to exclude certain patients at risk.

The transaminase elevation noted in only one case, requiring discontinuation of treatment, the latter was not considered since it is less than 5 times normal, a control performed after 48 hours showing liver function normal.

Other adverse effects have been reported by many authors such as cardiac disorders (bradycardia, QT enlargement, repolarization disorders, T-wave inversion with ST segment shift), liver injury (hepatic cytolysis or severe hepatocellular insufficiency) [6]; hematologic manifestations are possible (haemolytic anemia, agranulocytosis, thrombocytopenia, sometimes significant hemorrhages) but regressive. Note that these complications occurred only during the treatment of visceral leishmaniasis. In addition, renal toxicity is rare, related to a disorder of the concentration of urine without alteration of renal function. Cases of acute pancreatitis have been observed, mainly in immunocompromised patients (renal transplant recipients or those infected with the human immunodeficiency virus (HIV).

CONCLUSION

Based on the results obtained, the study that we reported is interesting in that it allowed us to highlight the adverse effects of systemic Glucantime®, which encourages the introduction of strict medical supervision during the administration of the treatment especially for the old persons.

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