SHORT COMMUNICATION
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Investigation of quality deviation in thiamine (vitamin B1) tablets due to suspect of therapeutic inefficacy in the treatment of neuropsychiatric conditions

Investigação de desvios de qualidade em comprimidos de tiamina (vitamina B1) devido à suspeita de ineficácia terapêutica no tratamento de condições neuropsiquiátricas

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ABSTRACT

Introduction: Thiamine supplementation for alcohol-dependent patients is one of the most important strategies for treating alcohol withdrawal syndrome and preventing and treating more serious neurological related complications. Also, it is used as adjuvant treatment for neurological conditions in geriatric patients. A municipal sanitary surveillance service from São Paulo requested the analysis of batches of thiamine hydrochloride tablets after complaints of therapeutic inefficacy during treatment of distinct neuropsychiatric conditions. **Objective:** To check if the thiamine therapeutic inefficacy complaints were associated to the medications' quality. **Method:** Fiscal analyses were performed including aspect, weight variation, identification and potency of thiamine hydrochloride, uniformity of unitary doses and dissolution. **Results:** There was no quality deviation in the medications, as all performed assays presented satisfactory results. **Conclusions:** The administration of quality medications is essential for obtaining expected clinical effects. Other factors not associated to the medication quality such as patients' adherence to the treatment and poor oral absorption might be associated to the complaints.

KEYWORDS: Thiamine; Fiscal Analysis of Products; Quality Control; Alcoholism; Nervous System Diseases

RESUMO

Introdução: A suplementação com tiamina em pacientes dependentes de álcool é uma das condutas médicas mais importantes no tratamento da síndrome de abstinência alcoólica e na profilaxia e tratamento de complicações neurológicas mais sérias, sendo também utilizada como adjuvante em quadros neurológicos em pacientes geriátricos. A Vigilância Sanitária de um município de São Paulo solicitou análise de lotes de comprimidos de cloridrato de tiamina devido a queixas técnicas de suspeita de ineficácia terapêutica no tratamento de condições neuropsiquiátricas distintas. **Objetivo:** Verificar se as suspeitas de ineficácia terapêutica da tiamina estavam relacionadas à qualidade dos medicamentos. **Método:** Foram realizadas análises fiscais contemplando ensaios de aspecto, variação de peso, identificação e teor de cloridrato de tiamina, uniformidade de doses unitárias e dissolução. **Resultados:** Não foram encontrados desvios de qualidade nos medicamentos, uma vez que todos os ensaios realizados apresentaram resultados satisfatórios. **Conclusões:** A administração de medicamentos de qualidade é indispensável para a obtenção dos efeitos clínicos esperados. Outros fatores não relacionados à qualidade dos medicamentos, como a adesão dos pacientes ao tratamento e prejuízo da absorção por via oral, podem estar relacionados às queixas.

PALAVRAS-CHAVE: Tiamina; Análise Fiscal de Produtos; Controle de Qualidade; Alcoolismo; Doenças do Sistema Nervoso

INTRODUCTION

Vitamins are essential for the human body. They contribute to normal growth, development and play an important role in human health[1]. Vitamins can be obtained through diet or supplementation. While the deficiency of some of them is related to some pathologies, high doses of vitamins can be harmful and should be avoided[2].

Thiamine (vitamin B1) is one of the vitamins that is most affected by alcohol consumption. Excess alcohol consumption is directly associated with lack of thiamine in the organism. Thiamine supplementation in patients addicted to alcohol is one of the most important treatments for the alcohol withdrawal syndrome. It also works for the prophylaxis and treatment of more serious neurological complications, like Wernicke-Korsakoff syndrome (WKS)[3].

Some studies suggest that thiamine could benefit the treatment of Alzheimer's disease, since it slows down the progression of dementia in WKS. Such a hypothesis considers that thiamine would have anticholinesterase activity, which would benefit Alzheimer's disease patients, since memory and some intellectual functions are mediated by acetylcholine[4].

The Health Surveillance Agency of a city in the state of São Paulo (SP), Brazil, asked the Adolfo Lutz Institute (Public Health Central Laboratory (LACEN/SP) to perform a fiscal analysis of two batches of thiamine hydrochloride 300 mg tablets distributed to the city public network due to suspicion of therapeutic inefficacy at different times.

The first technical complaint took place in a Psychological and Social Care Center - Alcohol and Drugs (CAPS-AD III). The complaint notification form described "suspected thiamine inefficacy due to neurological worsening in alcohol withdrawal syndrome patients".

The second technical complaint came from a Medical Specialty Outpatient Clinic. The complaint form described "suspicion of thiamine inefficacy due to neurological worsening in an elderly female patient", without further detail about the case.

Within the responsibilities of the Brazilian Unified Health System (SUS), the treatment of alcohol abuse is based on CAPS-AD. In the aforementioned city, CAPS and Basic Health Units (UBS) are where patients in the area of Mental Health go. Medical Specialty Outpatient Clinics are city health facilities that offer specialized medical treatment.

Reports of technical complaints must be evaluated taking into account the associated health risks in order to act in their investigation, with inspection, collection, fiscal analysis or even the adoption of preventive measures[5,6].

Deviations in medication quality may lead to therapeutic inefficacy due to changes in the product, ranging from confusing information on the label or package insert to changes in physical, chemical, biological or organoleptic properties[5,6].

Thus, the objective of this study was to check, based on suspected therapeutic inefficacy of thiamine, the quality of the drugs through pharmaceutical assays.

METHODS

Samples

Two batches of thiamine hydrochloride 300 mg tablets distributed in the city public health network involved in the technical complaints of therapeutic inefficacy, collected by the Health Surveillance agency.

Reagents

Hydrochloric acid, heptanesulfonic acid and triethylamine (Vetec/Sigma-Aldrich, Duque de Caxias, Brazil), methanol for HPLC and phosphoric acid (Merck, Darmstadt, Germany), ultrapure and distilled water (Elgastat Maxima Veolia, Paris, France) and secondary standard thiamine hydrochloride.

Assays

Product appearance

Done through visual inspection for the presence of a seal wrapping the packaging and nonconformities in the tablets, like cracks, foreign particles, crumbling or color changes.

Tablet weight variation

We evaluated the weight of twenty tablets with an analytical balance (Mettler Toledo Al204, Greifensee, Switzerland) and calculated the mean weight. A variation of up to ± 5% over the mean weight can be tolerated for up to two units, but none beyond its double[7].

Thiamine hydrochloride identification and content

Performed through representative sampling of the batches and analyzed in a high-performance liquid chromatograph equipped with an ultraviolet detector (HPLC-UV) (Waters, Milford, USA). The mobile phase was composed of a pH 3.2 mixture of heptanesulfonic acid, methanol and triethylamine. We used a C18, 25 x 4 mm, 5 µm (Macherey-Nagel, Duren, Germany) column with a 0.8 ml/min flow rate, 60 µl injection volume and λ = 246 nm at room temperature[7].

The identification of thiamine hydrochloride was performed by comparing the retention time of sample peaks and the standard in the chromatograms obtained, while the measurement of the content of the substance was performed by quantifying the samples in the face of a known concentration standard. We considered values between 92.5% and 107.5% of the amount to be satisfactory[7].

Uniformity of dosage units

By performing this test we verified the homogeneity of the active ingredient in the doses. We weighed ten tablets in order to check weight variation. We considered a variation of up to 15% (AV-acceptance value) to be satisfactory[7].

Thiamine hydrochloride dissolution

The tablet dissolution assay assesses the amount of dissolved drug in order to help predict its *in vivo* performance.

We tested six tablets in a dissolution device (Erweka DT 12R, Heusenstamm, Germany) using water as the dissolution medium (900 mL), paddles, rotation at 50 rpm and temperature of 37° C for 45 min. We evaluated the amount of thiamine hydrochloride by UV spectroscopy (HP/Agilent, Santa Clara, USA), λ = 246 nm, using water as blank solution. A minimum of 80% (Q + 5%) of the amount of dissolved thiamine hydrochloride was considered satisfactory[7].

RESULTS AND DISCUSSION

Preservation of the pharmacological action, in addition to a safe toxicological profile, is expected after the administration of a drug. The evaluation of the quality of drugs associated with suspected therapeutic inefficacy is one of the health surveillance agency responsibilities[6,8] and is performed with official laboratories in order to elucidate the events.

The tablets were packed in the original packaging of the manufacturer and showed no non-conformities. Samples were positive for thiamine hydrochloride. The table shows the sample test results.

The figure shows the chromatogram of the thiamine hydrochloride identification/content test (A) and the UV absorption spectrum found in the dissolution test (B).

The treatment of neuropsychiatric conditions associated with hypovitaminosis should aim at restoring vitamin levels as briefly as possible, thus leading to a lower risk of central nervous system disorders.

Patients addicted to alcohol have nutritional alterations of different levels of severity. When alcohol withdrawal occurs, nutritional requirements increase, and greater amounts of nutrients are required[9].

Alcohol withdrawal is a serious condition that poses risks to the patient's life, and thiamine replacement must be prioritized and done quickly in order to restore its levels adequately[9].

Thiamine supplementation is an essential intervention to treat and prevent the progression of symptoms related to its deficiency in patients addicted to alcohol and is also used as an adjuvant in neurological conditions in geriatric patients.

The investigation of complaints of therapeutic inefficacy must consider the quality of the drug, since the suspicion of quality deviation of the drug may just be the cause of the observed inefficacy[6,10].

In this study, we found no quality deviations in the drugs, since all the tests performed presented satisfactory results.

Bioavailability analysis, such as tests that evaluate the speed and extent of the absorption of thiamine, could contribute to a deeper investigation of the cases.

CONCLUSIONS

Alcohol addiction and neurological conditions in the elderly are complex pathologies, which makes it difficult to elucidate technical complaints. The administration of quality drugs is essential to obtain the expected clinical effects. Other factors unrelated to drug quality, like adherence of patients to the treatment and oral absorption loss may be related to complaints of suspected thiamine inefficacy presented in this study.

Table. Results of the assays performed on batches of thiamine hydrochloride tablets.

Assay	Site of the technical complaint		Reference value[7]	Result
	CAPS-AD	Medical Specialty Outpatient Clinic		
Weight variation[a]	-2.1% and +3%	-4.6% and +4.5%	<± 5%	Satisfactory
Thiamine hydrochloride content	96.2%	95.2%	92.5% -107.5%	Satisfactory
Uniformity of dosage units[b]	6.1%	8.8%	< 15%	Satisfactory
Dissolution	99.5%; 98.3%; 98.5%; 100.4%; 99% and 101.2%	90.9%; 91.2%; 82.6%; 95.5%; 92% and 88.3%	> 80%	Satisfactory

CAPS-AD: Center for Psychological and Social Care - Alcohol and Drugs.
[a] Relative to the mean weight expressed in minimum and maximum variation.
[b] expressed in AV-acceptance value.

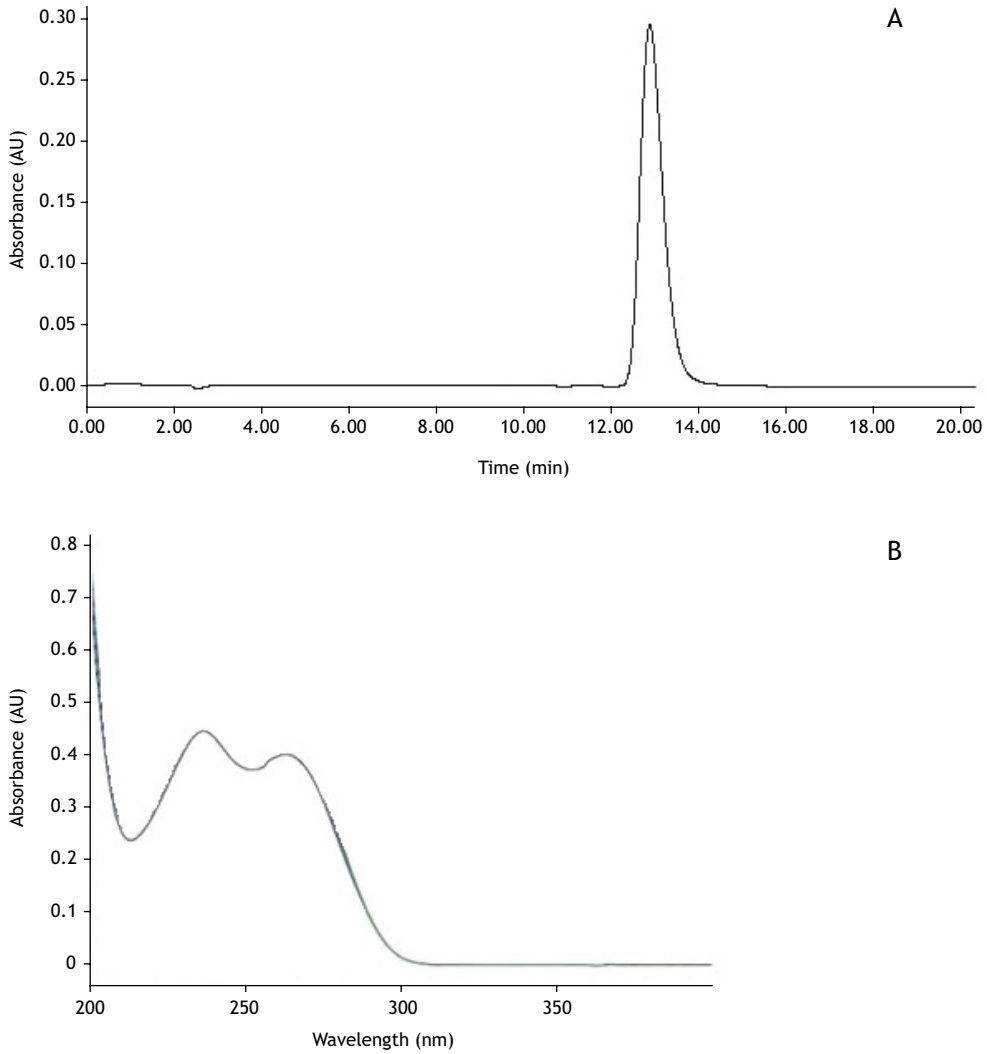

Figure. Chromatogram of the thiamine hydrochloride identification/content assay (A) and thiamine hydrochloride UV absorption spectrum (B).

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Conflict of Interest

Authors have no potential conflict of interest to declare, related to this study's political or financial peers and institutions.