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Adverse reactions to L-asparaginase in oncopediatric patients

Reações adversas ao medicamento L-asparaginase em pacientes oncopediátricos

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ABSTRACT

Introduction: Adverse drug reaction (ADR) is defined as "any harmful or undesirable and unintended response occurring with medicaments at doses usually employed in humans". **Objective:** To describe the adverse reactions to L-asparaginase, developed by oncopediatric patients, accompanied by the Pharmacy Clinic service, in a philanthropic hospital, in Salvador, Bahia, Brazil. **Method:** This is a cross-sectional, retrospective, descriptive study, in which an analysis of nine electronic medical records of oncopediatic patients was performed using L-asparaginase from June 2017 to February 2018. **Results:** Among the patients, 66.7% were male and 55.6% were aged ≤ 5 years. Acute lymphoid leukemia was the diagnosis of all patients. 66.7% of the study group presented some type of adverse reaction, pruritus being the most frequent (36%) and in 66.7% of the situations, the drug was suspended. All reactions were reported. **Conclusions:** The results suggest that special attention is needed in oncopediatric patients, since the possibility of adverse drug reactions is higher. With the performance of the pharmacist in centers of high complexity in Oncology, it is possible to develop strategies and promote actions to prevent or minimize the occurrence of these adverse events during antineoplastic therapy.

KEYWORDS: L-Asparaginase; Leuginase; Oncopediatrics; Acute Lymphoblastic Leukemia; Pharmacovigilance

RESUMO

Introdução: Reação adversa a medicamento (RAM) é definida como "qualquer resposta prejudicial ou indesejável e não intencional que ocorre com medicamentos em doses usualmente empregadas no ser humano. **Objetivo:** Descrever as reações adversas ao medicamento L-asparaginase, desenvolvidas por pacientes oncopediátricos, acompanhados pelo serviço de Farmácia Clínica, em um hospital filantrópico, de Salvador, Bahia, Brasil. **Método:** Trata-se de um estudo transversal, retrospectivo, descritivo, no qual foi realizada análise de nove prontuários eletrônicos dos pacientes oncopediátricos, em uso de L-asparaginase no período de junho de 2017 a fevereiro de 2018. **Resultados:** Entre os pacientes, 66,7% pertenciam ao sexo masculino e 55,6% apresentavam idade ≤ 5 anos. A Leucemia Linfoide Aguda foi o diagnóstico de todos os pacientes. Sessenta e sete vírgula sete por cento (66,7%) do grupo de estudo apresentou algum tipo de reação adversa, sendo prurido a mais frequente (36%) e, em 66,7% das situações, o medicamento foi suspenso. Todas as reações foram notificadas. **Conclusões:** Os resultados sugerem que é necessária uma atenção especial aos pacientes oncopediátricos, visto que a possibilidade de ocorrer reações adversas a medicamento é mais elevada. Com a atuação do farmacêutico nos centros de alta complexidade em oncologia, é possível desenvolver estratégias e promover ações para prevenir ou minimizar a ocorrência desses eventos adversos, durante a terapia antineoplásica.

PALAVRAS-CHAVE: L-Asparaginase; Leuginase; Oncopediátricos; Leucemia Linfoblástica Aguda; Farmacovigilância

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INTRODUCTION

Adverse Drug Reactions (ADR) are defined as "any unintended and deleterious or undesirable response to medicinal products at doses commonly used in humans for disease prophylaxis, diagnosis, treatment or modification of physiological functions"[1]. They may occur to a greater or lesser extent, early or late, acutely or chronically, depending on individual patient factors, exposure time and plasma drug concentration[2].

Medicines for children and teenagers should be administered with caution because of the difficulty finding accurate pharmacotherapy information for this specific population. Childhood is a heterogeneous age group that may have unpredictable pharmacokinetic behavior, and only some of the drugs given to these individuals have been the object of rigorous clinical studies[3].

The use of antineoplastic agents present in therapeutic protocols for childhood cancer, such as L-asparaginase in the treatment of acute lymphoblastic leukemia (ALL), which accounts for about 30% of all childhood neoplasms, is associated with hypersensitivity reactions, as a result of aggressive and prolonged treatments[4].

L-asparaginase is a standard agent in protocols used in pediatric patients diagnosed with ALL[5]. It is the first enzyme with antileukemic activity and it is responsible for causing the death of malignant cells through enzymatic cleavage of the L-asparagine amino acid circulating in aspartic acid and ammonia, due to these cells' inability to produce this compound[6,7]. Studies indicate that there are adverse reactions (AR) related to this drug in 30% to 60% of the cases, although there is no defined percentage for the occurrence of these adverse events[8].

The data obtained in this evaluation aim to contribute to the clarification of these reactions and to improve the care plan of pediatric cancer patients. Therefore, the objective of the present study was to describe the AR to L-asparaginase in pediatric cancer patients, accompanied by the clinical pharmacy service in a philanthropic hospital in Salvador, state of Bahia, Brazil.

METHOD

This is a cross-sectional, retrospective, descriptive study aiming to analyze the AR occurring in pediatric cancer patients taking L-asparaginase (Leuginase) from the clinical pharmacy service of the oncology sector of a philanthropic hospital located in Salvador, Bahia, Brazil, from June 2017 to February 2018.

Data were collected from electronic medical records. This enabled the evaluation of 28 records, of which nine pediatric cancer patients were aged 0-19 years and were in a treatment protocol containing L-asparaginase during the timeframe determined for the research. This study was approved by the Ethics Committee for Research on Human Beings under opinion n. 2.750.248.

RESULTS

According to the results obtained, of these nine patients, 66.7% were males and 33.3% were females. As for their ages, they were divided into two groups: ≤ 5 years (55.6%) and> 5 years (44.4%). Regarding ethnicity, about seven (77.8%) were declared "pardo". Regarding the location of their households, 22.2% of the patients lived in Salvador and the others came from other locations in the state of Bahia (Table 1).

Regarding their primary diagnosis, ALL was prevalent in these patients. Eight cases (88.9%) were of the B cell line (Table 2). In addition, it was classified according to the International Classification of Diseases (ICD-10) and represented group C91.0. The proposed chemotherapy protocols are also described in Table 2. GBTLI-2009 stands out as the most prescribed treatment line.

AR in the presence of L-asparaginase occurred in six (66.7%) patients. Causality was determined in all cases through the Naranjo algorithm, which is a tool consisting of ten questions, whose purpose is to classify AR to drugs in probability categories: definite, probable, possible or doubtful[9]. During the evaluation, the identified reactions were considered possible, according to the score they obtained. The types of reactions and their frequency are shown in the Chart. When taken alone, itching was observed in four (36%) patients and urticaria in three (27%).

All events were investigated by the pharmacist, based on the guideline for reporting AR in oncology designed by the Brazilian Society of Pharmacists in Oncology (SOBRAFO) together with the National Health Surveillance Agency (Anvisa)[9]. The events were considered as grade 2 infusion-related allergic reactions (moderate level). In these cases, the infusion is interrupted and the symptoms are treated, with prompt response from the patients. Subsequently, the cases were notified to Anvisa

Table 1. Sociodemographic characteristics of patients taking L-asparaginase (Leuginase).

Sociodemographic characteristics	n	%
Gender		
Female	3	33.3
Male	6	66.7
Place of origin		
Salvador	2	22.2
Other locations	6	66.7
Not reported	1	11.1
Ethnicity		
Pardo	7	77.8
Black	1	11.1
Not reported	1	11.1
Age		
≤ 5 years	5	55.6

n: absolute number.

Table 2. Type of acute lymphoblastic leukemia and treatment protocols present in the study.

Clinical features	n	%
Cell lineage (immunophenotyping)		
B Precursor	8	88.9
T Precursor	1	11.1
Chemotherapy protocol		
BFM-2002	2	22.2
BFM-2009	1	11.1
GBTLI-99	1	11.1

n: absolute number.

through the Health Surveillance Notification System (Notivisa), in charge of receiving reports of adverse events, incidents and technical complaints.

The route of administration was another evaluated factor, with more adverse events in the intravenous route – four (66.7%) – compared to the intramuscular route – two (33.3%). In 66.7% of the situations, L-asparaginase was suspended and the patients were no longer exposed to the drug.

DISCUSSION

L-asparaginase is an important component of the ALL treatment of pediatric cancer patients. Its use involves the combination with other agents, including methotrexate, doxorubicin, vincristine, prednisone, cytarabine, cyclophosphamide, mercaptopurine, and other drugs in their respective line steps of the treatment line[6,7,10].

Regarding the patients in the study, there was a predominance of males (66.7%) and patients aged ≤ 5 years (55.6%). These data corroborate the literature, since in another study ALL had a higher incidence in children aged 2 to 5 years, about 80%, and the male predominance was 56.3%[11].

ALL can be classified according to immunophenotype, that is, the expression of specific antigens (cluster of designation – CD) in cell populations of interest (lineage B or T) from the immunophenotypic characteristics of lymphoblasts[11]. In the present study, 88.9% of leukemias were type B. According to the literature[12], approximately 85% of ALL cases correspond to B cell progenitors. Identification of immunophenotypic subtypes directly assists in the prognosis and treatment of patients, also considering age and cytogenetic changes. Favorable genetic abnormalities associated with B precursors involve hyperdiploidy (over 50 chromosomes) and TEL-AML1 or t fusion (12:21). The former causes greater sensitivity of blasts to chemotherapy. In the latter patients are highly sensitive to asparaginase for reasons that are still unknown[13]. It is not possible to analyze these markers and the cure of patients, because the study is cross-sectional and not cohort, considered the most appropriate for this purpose.

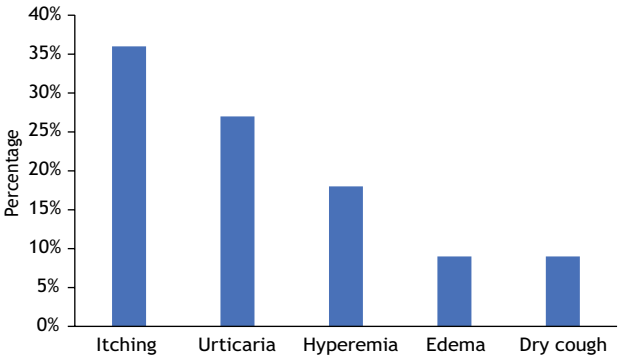

Chart. Percentage of patients taking Leuginase who had adverse reactions.

The definition of therapeutic protocols for each patient involves several factors, from the characteristics of the individual to the disease stage. The greater the risk of recurrence, the more intensive the treatment. The research identified four different types of protocols: GBTLI-2009, GBTLI-99, BFM-2002 and BFM-2009, with higher frequency of GBTLI-2009.

The Brazilian Cooperative Group for the Treatment of Childhood Leukemia (GBTLI) is divided into two groups: low risk and high risk, considering patient age, baseline leukometry, whether or not they have genetic translocations, and peripheral blood leukocyte count on day 8 after start of chemotherapy[14]. In Berlin-Frankfurt-Munich (BFM), patients are stratified according to risk group (low, intermediate and high) and factors like age, baseline Central Nervous System involvement, baseline leukocyte count, presence of chromosome abnormalities, among other factors[15]. Therefore, both can be assigned to patients at different stages of the disease.

The long treatment period and intermittent dosing regimens pose risks to patients, especially if these are pediatric patients, whose body is still maturing. Of the patients involved in the research, 66.7% had some type of AR during L-asparaginase use, in agreement with other studies[16], whose observed percentage was 60.5%. Clinical toxicity related to the use of L-asparaginase results from its antigenicity as a foreign protein and inhibition of protein synthesis[6,7].

The AR identified during the research were: urticaria (33.3%), edema (11.1%), itching (44.4%), dry cough (11.1%) and hyperemia (22.2%). L-asparaginase-related hypersensitivity reactions vary in severity, from localized transient erythema and injection-site rash to life-threatening acute anaphylaxis. The most common symptoms are pain, soreness, swelling, and erythema at the injection site when administered intramuscularly, and intravenous dyspnea, bronchospasm, itching, rash, and urticaria[17].

The route of administration is another important aspect that should be carefully evaluated before drug administration. The intravenous route was present in 66.7% of the cases of AR compared to the intramuscular route. Other studies[18] reported that, initially, there was an association of intravenous L-asparaginase and an increased incidence of hypersensitivity

reactions. However, other results have been found in recent years[19]: a percentage of 23.7% AR with intravenous L-asparaginase, involving 76 pediatric patients, that is, less than half of the population studied.

Pharmacists in the multidisciplinary team can provide more qualified patient care, since these professionals, in their scope of actions with integrated focus on the patient, work to avoid or minimize problems related to pharmacotherapy, especially in antineoplastic therapy. This is particularly relevant to the treatment of pediatric patients, due to their higher risk of having AR either because of physiological immaturity or the aggressiveness of the proposed treatment[20].

In this context, by applying pharmacovigilance tools, pharmacists have been making a fundamental contribution to the detection of ARs to drugs and risk factors for their emergence. Moreover, pharmacists help design actions to prevent the occurrence of these events and thus provide safer treatment to pediatric cancer patients[8].

Notification of all ADR (even moderate cases) to the responsible agency directly contributed to the evaluation of the post-marketing phase of the L-asparaginase (Leuginase) drug from Beijing/Xetley, since it was still in the process of approval by Anvisa[21]. There was, therefore, the need for greater surveillance during the period of use of this specific therapy by patients, in order to early identify any problems related to it.

CONCLUSIONS

L-asparaginase is a fundamental component in the treatment of pediatric cancer patients diagnosed with ALL, but the AR caused by the drug may make its use unfeasible.

The notification of AR to the health surveillance agency contributes to a more qualified follow-up of the drug in the post-marketing phase and, consequently, to the pharmaceutical industry's improvement. The greater the number of notifications by different institutions, the greater amount of data is collected, which can help improve the process. Additionally, reporting the occurrence of ADR, especially when there is lack of information in the literature, may raise the awareness of health teams and even generate further meta-analyses.

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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.