ADVERSE REACTIONS TO AMPHOTERICIN B IN ADULTS - DATA MINING

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ABSTRACT

Background: Amphotericin B deoxycholate (d-AmB) is a drug widely used in fungal infections. The adverse effects of this medicine may be acute (infusion-related) or late (cumulative dose-related). **Objective**: This study aims to evaluate the frequency of adverse reactions to amphotericin B deoxycholate (d-AmB) in adults in a University Hospital, describe the profile of drug use in the institution and evaluate the factors related to the development of reactions with the aid of data mining. **Methods**: A database with the characteristics of the patients and information about the adverse reactions was created. Then, data mining was performed with the aid of WEKA software. **Results**: Fifteen adult patients who had used d-AmB in the selected period were identified, being 60% male. The mean age was 41.8 years old. Only 6 patients concluded their treatments with d-AmB, the others had to interrupt the treatment due to some intercurrence. Among the acute phase reactions, the most frequent were vomiting, nausea, phlebitis, hyperthermia and headache, which were related to the drug infusion. As for subacute reactions, the most frequent were urea and creatinine elevation, and hypokalemia. 30 rules were identified after data mining: d-AmB longer-term use, even with normal initial creatinine and urea, they had a greater number of acute reactions; patients with no creatinine change during d-AmB treatment had less subacute reactions; higher number of nephrotoxic drugs use, in those with increased creatinine, they presented a greater number of subacute reactions. **Conclusions**: The results demonstrate that there is a relation between the time of use and the greater number of adverse reactions. This safety data help clinicians to make decisions.

Keywords: Amphotericin B, Adults, Adverse reaction, Data mining

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INTRODUCTION

Fungal infections are increasingly prevalent, especially in cases of febrile neutropenia, immunosuppression, transplantation and in users of high doses of corticosteroids or in those undergoing abdominal surgeries or intravascular catheters [1-5].

The clinical use of Amphotericin B deoxycholate (AmB-d) occurred after the 1960s, after the extraction of an actinomycete that inhabits the soil, the *Streptomyces nodosus* [6]. Such a drug has broad spectrum action and efficacy against fungi and protozoa [5].

The antifungal activity of AmB-d depends on the binding of the sterol to the ergosterol present on the membrane of sensitive fungi [6]. The interaction between the AmB-d (hydrophobic portion) and the fungus membrane and some protozoa (genus *Leishmania* and amoebas) promotes the formation of pores increasing the permeability of the membrane, consequently extravasation of intracellular substances, leading to cell death [5,7]. It also produces oxidative stress that results in metabolic alterations detrimental to cell survival [6].

In addition, AmB-d has a proinflammatory effect due to stimulation of the production of inflammatory cytokines through the *toll-like receptor* (TLR)-2, which will trigger a T *helper*-1 type immune response (Th1). Consequently it will lead to the activation of macrophages and the production of superoxides and nitric oxide, which will make the individuals have a better response to the fungal infection. However, this mechanism is also responsible for infusion reactions and exacerbated reactions in non-immunosuppressed patients [5].

This drug has a narrow therapeutic index. Adverse effects may be related to infusion - acute reactions - for example: fever, chills, phlebitis, nausea, vomiting, headache, among others; or late effects - subacute reactions - for example: anemia, thrombocytopenia, leukopenia and renal toxicity [5]. The late adverse reactions are related to the cumulative dose received and the patient's sensitivity and organic conditions [6].

The main adverse reaction related to the use of AmB-d is renal damage, in most cases associated with hypokalemia, due to decreased renal blood flow (severe vasoconstriction) and direct renal tubular toxicity (interaction with kidneys of the kidneys' epithelial cells) [5,8]. For prevention measures such as infusion of one liter of saline containing 1 vial of 19.1% KCl in 2 to 4 hours before infusion of the drug are necessary; potassium-rich diet and oral KCl supplementation after infusion of the drug [9]. The AmB-d should be administered in glycosated serum to avoid precipitation thereof [6].

The risk of nephrotoxicity is reduced by up to 50% with lipid formulations, but the cost is higher. These formulations are options for those patients intolerant of the conventional drug or who cannot withstand the conventional formulation due to

alteration of renal function [7]. Despite the adverse reactions, AmB-d continues to be used due to its broad spectrum against filamentous fungi and yeast, known toxicity profile, and relatively low cost [4].

Due to the large number of adverse reactions to AmB-d reported in the literature, the objective of this study was to evaluate the profile of the use of such drug in the institution and to evaluate the factors related to the development of adverse reactions with the aid of data mining techniques.

METHODOLOGY

This is a cross-sectional, descriptive study with retrospective data collection, carried out in a general public university hospital in the Western State of Paraná (HUOP). The research was approved by the research ethics committee of the State University of Western Paraná under number 1,696,944.

With the aid of the computerized system of the hospital, a movement report (distribution to the infirmary) of the AmB-d was generated in the period from 11/11/2014 to 03/31/2016, which contained the patient's name and ward. For inclusion in the study, the patient should be adult (> 18 years) and have used more than one dose of AmB-d in the period to be evaluated.

The data for analysis were obtained from the physical records available in SAME (Medical File Service) and electronic medical records. The variables (number of patient care, age, gender, hospitalization ward, pathology that led to hospitalization, weight, comorbidities, smoking, alcoholism, initial laboratory tests, laboratory tests altered during drug use, type of adverse reaction/or subacute), nephrotoxic drugs used concomitantly with AmB-d and outcome (discharge or death) were collected with the help of a structured questionnaire and organized into a database in the Excel® program. To define the nephrotoxic drugs used by the patients, the MICROMEDEX® database was used [10]. Descriptive statistical analysis was performed on the profile of the use of AmB-d in HUOP in the selected period.

KDD process

Data stored in the Excel® database can hide similarities that cannot be detected. Due to this the KDD process was used, *Knowledge discovery in database*, which comprises a technique used to identify such previously unknown information and extract it from the dataset, allowing strategic decision-making [11-12].

The KDD process consists of five steps: selection, preprocessing, transformation, data mining (MD) and interpretation of results [13].

Selection of data

This is the first phase of the KDD, in which the data set to be analyzed is chosen [14-15]. This set was obtained from the tabulation of the data collected from the charts of patients selected for the study. The chosen database contained 22 attributes, of which 11 were numeric and 11 were nominal. The numerical attributes are: age, days of hospitalization, initial urea, initial creatinine, initial potassium, initial sodium, urea change, creatinine change, potassium change, sodium change, time of use on AmB-d days. The nominal attributes are gender, comorbidities, smoking, alcoholism, subacute reactions, acute reactions, acute kidney injury (ARI), suspension of AmB-d treatment, infection during use of AmB-d and use of other nephrotoxic drugs concomitant with d- AmB.

AmB-d treatments, called instances, were used for data mining. The number of instances must be representative of the class in question and allow the chosen algorithms to generate valid decision rules. Thus, there is no limiting data number for the MD technique decision tree [14].

Pre-processing of data

This phase is intended to ensure the quality of the selected data [14-15]. In this stage, classes for certain attributes were defined: comorbidities (numerical quantification in how many comorbidities the patient had), laboratory tests (the numerical values found were defined as "normal", "increased", "low", according to the value of hospital referral for each examination), subacute and acute reactions were numerically quantified, as well as nephrotoxic drugs used during treatment with AmB-d.

Data transformation/Formatting

After the above steps, the database was saved in comma-separated format (csv) [14-15], for further analysis in *software* open source technology WEKA (*Waikato Environment for Knowledge Analysis*), version 3.8.0. The WEKA comprises a collection of learning algorithms for MD tasks made available by the GNU (General Public License) through the University of Waikato [16]. The *software* WEKA analyzed the data through descriptive statistics, providing minimum value, maximum value, mean and standard deviation for numerical attributes.

Data mining

The data mining is one of the KDD processes, where it is possible to extract rules that allow to relate the various variables of the study [13-16]. For the realization we chose the use of the WEKA algorithm J48, which allows the definition of patterns in the form of decision tree. A tree consists of an ordered pattern of concepts, starting at a root node, each concept being subdivided into sub-concepts at the lower level of the tree. Each terminal element of the tree is associated with an objective concept and is known as leaf node [13]. This analysis serves to verify the similarity relations between the information.

Interpretation of results

Each leaf node found in the previous step has been interpreted, evaluated, generating relevant information.

Definition and classification of Acute Renal Injury

To determine whether the patient developed acute renal injury (AKI), the definition of AKI proposed by the International Society of Nephrology and the acute kidney injury guideline of the Brazilian Society of Nephrology [17-18].

According to KDIGO and YU *et al*, AKI stage 1 is defined as an increase in serum creatinine (Cr) of 0.3 mg/dl in 48 hours or increase of 1.5-2-fold in 7 days. AKI stage 2 is defined as being an increase> 2-3 times the baseline value of CR. Stage 3 AKI is defined as a>3-fold increase in CR or ≥ 4 mg/dL with an acute increase of at least 0.5 mg/dL. Patients on dialysis are considered stage 3 [17-18].

RESULTS

In the assessed period, 29 patients who used AmB-d between children and adults were identified. Of these, only 15 patients met the inclusion criteria and had their charts analyzed. However, 17 treatments with AmB-d were analyzed, considering that 2 patients did two treatments with the drug at different time intervals.

From the sample universe (n=15), 60% (n=9) were male. The mean age of the studied group was 41.8 (11.3) years. Among the male patients, the mean age was 42.4 [6.4] years and among the women the mean was 40.8 [17.1] years.

A mean length of hospital stay was 43 days, the shortest time being 11 days in the medical and surgical clinic and the highest 106 days in the G-ICU.

The reasons patients were hospitalized included pancytopenia (n=1), cutaneous mucosal leishmaniasis (n=1), external hemorrhoids (n=1), pleural effusion (n=2), hepatosplenomegaly (n=1), neurotoxoplasmosis (n=1), acute lower abdomen (n=1), headache and seizures (n=1), neurotoxoplasmosis (n=1), level of consciousness (n=1) and cerebral abscess (n=1).

Among the health problems associated with the patients selected for

the study, there were: (N=1), syphilis (n=1), malaria (n=1), dyslipidemia (n=1), hypothyroidism (N=1), herpes zoster (n=1), anemia (n=1), low belly pain (n=1), epilepsy (n=1), systemic arterial hypertension, chronic sinusitis (n=1) and gastric ulcer (n=1).

Only five patients had no associated comorbidities. As for steroid therapy only one was in use a week ago.

Of the total of 15 patients with indication for AmB-d use, two were indicated empirically. Of these, one patient discontinued the use of AmB-d as soon as he discarded hypothesis of fungal infection and the other continued treatment due to febrile neutropenia. Two had indicative of the use of AmB-d due to the biopsy evidencing leishmania, being one of these visceral leishmaniasis and another cutaneous leishmaniasis. One patient used AmB-d due to the presence of *Paracoccidioides* spp. on the biopsy. Five patients used the drug in question for treatment of neurocryptococcosis with *Cryptococcus neoformans* evidenced by examinations such as CSF culture, blood culture, Chinese ink and serology. Three treatments were due to presence of yeast structures, verified through blood culture, catheter tip culture and biopsy. There was a treatment for *Candida glabrata* and a treatment did not have the agent identified, but on the magnetic resonance of the skull, parenchymal lesions suggestive of infectious (fungal or tuberculin) etiology were observed.

All treatments lasted longer than 72 hours. The mean time of use was 12 days and the lowest treatment was 3 days and the highest was 21 days.

As for patients who received two AmB-d treatments in different time intervals, one of them had to stop the first treatment due to adverse reactions to the drug, but 12 days later it restarted due to persistence of fever and neutropenia. After 9 days on the second treatment the drug had to be discontinued due to acute renal injury. The other patient who did 2 treatments also had to stop the first treatment and restarted 12 days later. After 17 days on the second treatment, the drug had to be discontinued because of a significant change in creatinine.

All the patients analyzed received a dose of 50mg/day, except for one patient who received 30mg/day.

As for the 17 treatments performed with AmB-d, 6 were complete, 4 were suspended due to acute renal damage, 3 were suspended due to adverse reaction to the drug, 1 needed antifungal replacement (started to use liposomal AmB), 2 cannot be concluded because the patient died during treatment and 1 was suspended due to fungus negative culture.

Of the total number of patients, 5 (33.3%) had AKI stage 1, 2 (13.3%) AKI stage 2, 1 (6.67%) AKI stage 3 (requiring dialysis), and 7 (46.7% %) had no acute renal injury (even with elevated creatinine). Of the patients who did 2 treatments, only 1 presented AKI (stage 2), in the second treatment. Of all patients (n=8) who had this adverse event, 50% had AmB-d administration suspended.

For those with AKI, the *software* WEKA generated a decision tree regarding the suspension or non-treatment based on creatinine and time of use of this antimicrobial in days (Figure 1), with 100% accuracy and all instances correctly classified.

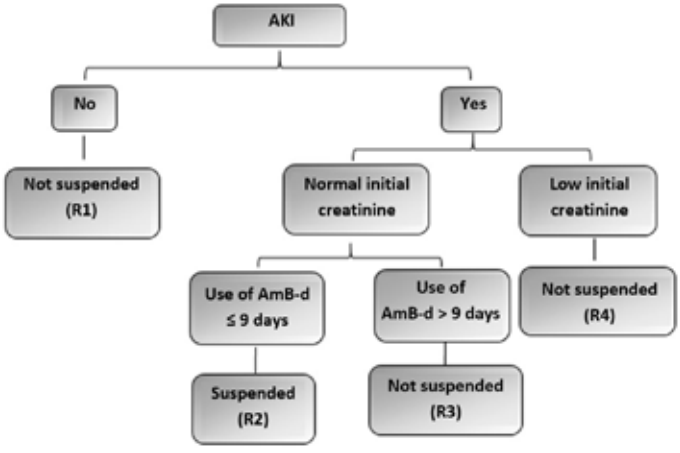


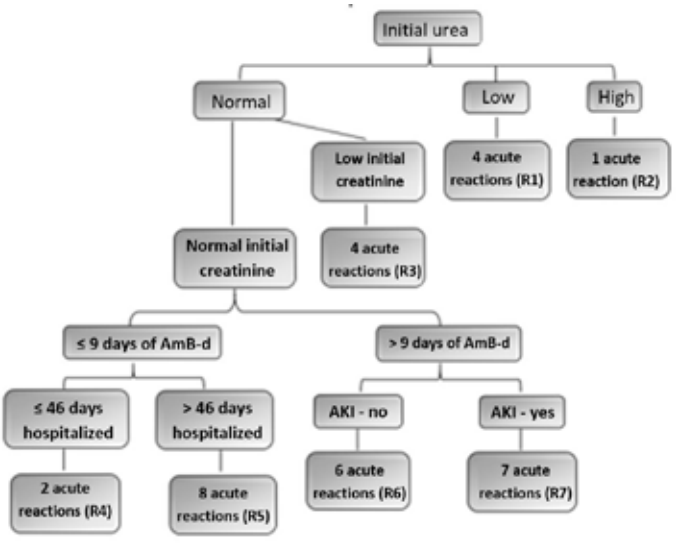
Figure 1: Decision Tree for Suspension of AKI-Based AmB-d Treatment

The decision tree of Figure 1 generated four decision rules (R) for the evaluated meta attribute. Thus, it is observed that the development of acute renal injury in the evaluated patients was an important factor for the interruption of the treatment. Patients who did not develop AKI did not discontinue treatment (R1). Rule 4 (R4) classified those who had low initial creatinine and who progressed to AKI, but as they did not present complications, it was not necessary to discontinue treatment. The R 2 and R 3 rules, however, classified patients who had normal creatinine before using AmB-d and who progressed to AKI, but in these cases renal changes were observed in a time ≤ 9 days, and then the treatment was suspended.

Decision rule 2 (R2) shows that in susceptible patients with AmB-d treatment time of less than 9 days, AKI is detected, and treatment discontinued.

As for the acute reactions resulting from the use of AmB-d, 28 different reactions were identified, totaling 76 occurrences between men and women, with an average of 5 (3.78) reactions per patient. The most frequent acute reactions were vomiting (47%), nausea (40%), phlebitis (40%), followed by hyperthermia (33%) and headache (33%).

For acute reactions, the WEKA software generated a decision tree based on the meta attribute "acute reactions according to urea and creatinine before starting treatment with AmB-d (Figure 2), with 82.35% accuracy and 14 instances correctly classified.



Classification rules	Description
R1	Patients who had initial urea below the reference value had 4 acute reactions during the use of AmB-d
R2	Patients who had initial urea above the reference value had 1 acute reaction during the use of AmB-d
R3	Patients who had initial urea within the reference value and initial creatinine below the reference value had 4 acute reactions during the use of AmB-d
R4	Patients who had urea and initial creatinine within the reference value, used AmB-d ≤ 9 days and were ≤ 46 days in hospital, had 2 acute reactions during the use of AmB-d
R5	Patients who had urea and initial creatinine within the reference value, used AmB-d ≤ 9 days and were> 46 days hospitalized, had 8 acute reactions during the use of AmB-d
R6	Patients who had urea and initial creatinine within the reference value, used AmB-d > 9 days and did not develop AKI, had 6 acute reactions during the use of AmB-d
R7	Patients who had urea and initial creatinine within the reference value, used AmB-d > 9 days and developed AKI, had 7 acute reactions during the use of AmB-d

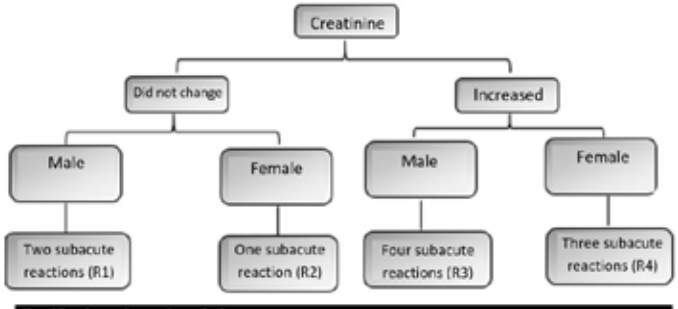
Figure 2: Tree and decision rules for acute reactions according to urea and creatinine before starting treatment with AmB-d

Patients who used a longer AmB-d time, even with creatinine and initial urea within the reference values and who had AKI, had a higher number of acute reactions (R7). According to the decision tree generated for acute reactions, it can be observed that a longer time of hospitalization leads to an increase in the number of acute reactions,

even in patients with normal urea and creatinine and with time of use of AmB-d less than 9 days (R5).

Concerning subacute reactions, of the 17 treatments evaluated 88% (n=15) presented hypokalemia, one patient did not have potassium altered during treatment and one patient presented hyperkalemia. Regarding the alteration in urea and creatinine, in 59% (n=10) of the treatments the patients presented elevation in these markers. Another electrolyte with significant alteration was sodium, 41% of the treatments (n=7) presented increase during treatment with AmB-d, 41% decrease in serum sodium and 18% (n=3) of the treatments did not change. In 2 treatments a decrease of hemoglobin could be observed and in 1 treatment there was severe thrombocytopenia.

The WEKA software generated a decision tree (Figure 3) for the meta attribute: "subacute reactions", based on creatinine change over AmB-d treatment, with 70.59% accuracy and 12 instances correctly classified.



Classification rules	Description
R1	If creatinine did not change during AmB-d treatment and the patient was male, he had two subacute reactions
R2	If creatinine did not change during treatment with AmB-d and the patient was female, she had a subacute reaction
R3	If creatinine increased during treatment with AmB-d and the patient was male, he had four subacute reactions
R4	If creatinine increased during treatment with d-AmB and the patient was female, she had three subacute reactions

Figure 3: Decision Tree and Rules for Subacute Reactions According to Change in Creatinine

In figure 3, it can be concluded that patients who did not have creatinine alteration throughout the treatment (R1 and R2) with AmB-d presented less subacute reactions. Similarly, female patients had fewer subacute reactions than men in both situations.

The fourth decision tree generated had the meta attribute "relationship between subacute reactions and creatinine alteration", with accuracy of 88.23% and 15 instances correctly classified. The main decision rule of this tree revealed that those patients who had a greater number of subacute reactions also had creatinine increase during AmB-d treatment.

Figure 4 represents a decision tree with accuracy of 76.47% and 13 instances correctly classified. It uses as meta attribute the relation of the subacute reactions and the levels of sodium.

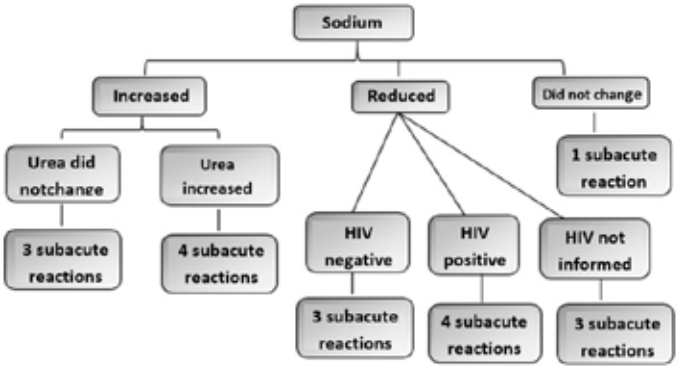


Figure 4: Decision tree for the attribute subacute reactions according to sodium levels during treatment with AmB-d

Figure 4 shows that patients who presented sodium and urea above the reference values used in the hospital during AmB-d treatment had a higher number of subacute reactions when compared to the others. HIV-positive patients with sodium below the reference values during AB treatment also had this profile.

All patients in the study used other nephrotoxic drugs concurrently with the use of AmB-d. Of the 17 treatments with AmB-d, 10 were performed in men, who had 19 prescribed different nephrotoxic drugs. Already in the women (7 treatments), 15 different nephrotoxic drugs prescribed concomitant with the antimicrobial in question were identified. We identified 23 different nephrotoxic drugs prescribed, with an average of 3.76 nephrotoxic drugs per treatment. The most prescribed nephrotoxic drugs were Omeprazole 14% (n=9), Ranitidine 14% (n=9), Cefepime 9% (n=6), Meropenem 6% (n=4), Norepinephrine 6% (n=4) and Enalapril 6% (n=4). Vancomycin was prescribed concomitantly with 2 treatments with AmB-d.

For nephrotoxic drugs as a meta attribute, a decision tree was generated, with accuracy of 82.35% and 14 instances correctly classified (Figure 5).

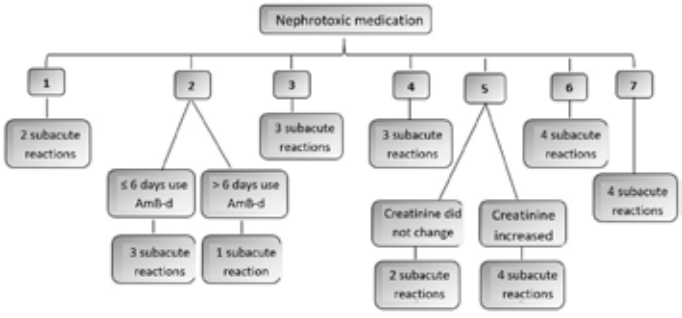


Figure 5: Decision tree for attribute subacute reactions, considering the nephrotoxic drugs used concomitantly to AmB-d

Figure 5 lists how many nephrotoxic drugs the patient used concomitantly with AmB-d and may have contributed to exacerbation of adverse reactions. Concerning subacute reactions, it can be observed that the higher the number of nephrotoxic drugs used, the more subacute reactions the patient presented in patients with creatinine above the reference values during the use of AmB-d. It is also noted that when patients used more than 2 nephrotoxic drugs the appearance of subacute reactions occurred within a period of less than 6 days.

Regarding the outcome of the treatments, 9 (60%) of the patients were discharged from hospital and 6 (40%) of the patients died.

DISCUSSION

In this study, most of the patients were male, which agrees with the work of Falci and Pasqualotto, which shows that male gender is a risk factor for developing nephrotoxicity to AmB-d [5]. Roxanna *et al.* also found in the evaluated population that 66.7% were males with a mean age of 45 years [4].

Fungal infections often occur in transplant patients, chemotherapy patients, patients with severe neutropenia, hematological malignancies and AIDS [19]. Among the sample universe evaluated in this study there were patients with these characteristics.

When analyzing the indication of AmB-d for the evaluated patients, we verified that all the treatments were according to the literature.

Regarding the duration of treatment with AmB-d, it was found that the results of this study resemble those of Roxanna *et al.* who performed a study in Chile and found that the duration of the treatment had on average 12 days [4].

Regarding the doses of AmB-d, these could not be judged as adequate or not, due to the difficulty in obtaining the patients weight. Only 4 patients had this information described in the medical record. The fact that the study is retrospective limits the obtaining of this data directly with the patient in the bed. According to Micromedex® AmB-d doses should not

exceed 1.5mg/kg/day [10]. Of the 4 patients who had this information described in the medical record, all were dosed within the safety interval.

The acute reactions are related to the perfusion of the drug and the release of TNF-α and IL-6, with the main reactions being fever, chills, arthralgia, nausea, vomiting, headaches and hypotension (5,20,22). The acute reactions most prevalent in this study corroborate those of Roxanna *et al.,* who found fever (25%), vomiting (15.2%) and phlebitis (6.7%) [4].

According to the criteria established by KDIGO and Yu *et al.,* the AKI data of the patients included in this study resemble those found by Rocha *et al.,* which evaluated 120 patients using AmB-d, and it was observed that 28.3% of the patients presented AKI stage 1, 20.8% of the patients presented AKI stage 2 and 10.8% of the patients presented stage 3 AKI [17,18,21].

Regarding the time of use of AmB-d and the development of renal injury, patients who used for a period of less than 9 days and developed AKI required treatment suspension. This is because AmB-d causes direct renal vasoconstriction, leading to a profound reduction of renal blood flow and changes in the membrane permeability of renal tubular cells, which trigger diffusion of hydrogen ions impairing acid excretion [21]. As found in the fourth decision tree, renal function impairment is predisposing to subacute reactions, with AmB-d being excreted via the kidney, and patients with impaired renal function are at increased risk of adverse drug reactions that are eliminated by this organ [10,23].

Renal damage triggered by AmB-d is manifested by elevated serum creatinine, whether accompanied by metabolic acidosis, as well as by hyperchloremia, hypokalemia and hypomagnesaemia [21]. Hypokalemia secondary to urinary potassium loss is one of the main adverse effects of AmB-d therapy and manifests itself in more than 25% of users [20,24]. In this study, 59% of the patients had creatinine and urea elevation and 88% of the patients had hypokalemia with the use of AmB-d. It should be emphasized that renal damage is usually reversible after discontinuation of the drug but may take a few weeks [20].

Hematological toxicity by AmB-d is very common, it is estimated to occur in up to 24% of treated patients and in those who take the drug for more than 30 days, anemia occurs in 95% of cases [5]. In this study, 13% (n=2) of the patients presented hemoglobin levels, one of them used the drug for 19 days and the other used for 21 days. Anemia associated with AmB-d is linked to a disturbance in the production of erythropoietin. Changes such as leukopenia and thrombocytopenia may also occur, but they are rarer and have a clinical impact to be evaluated [5]. Of the patients evaluated, 1 patient (7%) had severe thrombocytopenia, which used the drug for 18 days.

All the patients analyzed used other nephrotoxic drugs that may have potentiated renal damage. The use of drugs such as aminoglycosides, vancomycin, cyclosporine, corticosteroids, NSAIDs, cisplatin, among others, is an important risk factor for AmB-d induced nephrotoxicity, if caution is needed [6,20,24]. Berdichevsky evaluated low-risk patients and found that the use of nephrotoxic drugs, especially antibiotics, was associated with the development of AKI [6]. This adverse reaction is an independent risk factor contributing to the death of individuals [19]. Thus, data mining allowed us to gather factors that predispose to subacute lesions such as length of hospital stay, higher values of creatinine, sodium, urea, seropositive patients and presence of two or more nephrotoxic drugs.

The present study presents some limitations such as the difficulty of obtaining some information in the medical records (weight, HIV positive or not) and lack of medical evolution in the electronic medical record, which have made some analyzes limited.

CONCLUSION

In the sampled sample, it can be concluded that the male population, young, and with high HIV prevalence are the most predisposed to have adverse reactions to AmB-d.

Patients who use AmB-d for a longer time, even with normal initial creatinine and urea, and who have AKI, present a greater number of acute reactions, with the most prevalent being vomiting, nausea, phlebitis, hyperthermia and headache. The main subacute reactions in a population like this one are elevated urea and creatinine, and hypokalemia. Patients who have increased creatinine during AmB-d treatment have a greater number of subacute reactions. The female population has fewer subacute reactions, regardless of creatinine clearance. Increased sodium and urea during treatment with AmB-d also leads patients to have more subacute reactions.

The higher the number of nephrotoxic drugs used by patients with increased creatinine during AmB-d use, the greater the number of subacute reactions presented. Changes in creatinine lead to an increase in hospitalization time, an increase in costs related to patient care and the risk of death.

Studies such as these contribute to pharmacovigilance actions and provide safety data, assisting clinicians to make decisions at the time of prescription, as well as the drug and therapeutic committee in aiding the inclusion or exclusion of new technologies from standardized drugs in the institution. These data allow us to evaluate the need to include new technologies for certain population groups. Studies are needed to evaluate the quality of life of patients who are discharged from hospital when using AmB-d, due to the consequences that this drug can have on the body.

Finalcial Source

The authors declare that the research did not receive financing for its realization.

Conflict of Interests

The authors declare that there is no conflict of interest.

Authors' Contributions

ASL and ACCS: Full contente - design and planning of the research project; obtaining, analyzing and interpreting data; writing and critical review. Final approval of the version to be published. Responsible for all aspects of the work in ensuring the accuracy and integrity of any part of the work. DJ: Part of the content: obtaining, analyzing and interpreting the data. JGM: Part of the content: design and planning of the research project; obtaining, analyzing and interpreting the data.

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