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Full Length Research Paper

Medication use history in patients admitted to a teaching hospital: A cross-sectional study

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Although the literature shows several studies on medication safety, there are few Latin American studies describing aspects in the practice of medication reconciliation carried out by pharmacists in the admission process. This study aimed to describe the acquisition of medication use history of patients during admission, and to characterize the unintentional discrepancies in their pharmacotherapy in a Brazilian teaching hospital. This cross-sectional study was conducted within the University Hospital of the Federal University of Sergipe. Pharmacist-researchers collected patient data in four steps through a structured questionnaire developed by the researchers and adapted from the literature. After collection, the pharmacist-researcher and pharmacy students analysed the data and assessed if there were any unintentional discrepancies. The present study defined unintentional discrepancies (UD) as the unjustified variations between the patient’s previous medication use history and the pharmacotherapy prescribed during hospitalization. In this study, 358 patients were included. Of all patients, 261 (72.90%) were adults with the mean age of 47.16 ± 18.80 years. In 117 cases of adult patients (44.82%), there was no record of previous pharmacotherapy, and 137 (52.49%) were not questioned about their allergies. A total of 327 UD were found in 150 patients (41.90%). Of these UD, omission was the most common type, followed by different doses, erroneous frequency, and unjustified start of treatment. This study revealed the prevalence of unintentional discrepancies in the studied hospital, and points out that the assessment of the history of medications used is a complex practice, in which the pharmacist can be an ally.

Key words: Patient safety, medication errors, medication discrepancies, medication reconciliation.

INTRODUCTION

Adverse drug events are a worldwide concern in the healthcare system. Studies have reported that such
failures range from 45 to 76% with most occurring on admission due to unreliability on medication histories (Cornish et al., 2005; Bell et al., 2011). Medication reconciliation (MR) has been defined as a process that enables for the compilation of the most accurate medication list for a patient and proven to significantly reduce the rate of discrepancies in the pharmacotherapy. This list combines previously used drugs and the ones prescribed on admission, providing the correct medications for the patient anywhere in the hospital. Besides, MR has been associated with correction of medication history errors with clinical significance in up to 59% of cases (Mueller et al., 2012; Kwan et al., 2013).

Acquisition of a best possible medication history (BPMH) on admission is a critical step in MR, and the identification of medication discrepancies on admission may be an important factor to avoid errors and damages to the patients (Zed, 2015). However, MR has high complexity and requires resource intensity in order to achieve effective results (Pevnick et al., 2016). Therefore, the identification of unintentional discrepancies is a process that should be improved before MR implementation. Although the literature shows several studies about MR, there are few Latin American studies describing aspects in the practice of MR carried out by pharmacists in the admission process. So, this study was conducted to describe the acquisition of medication use history of patients during admission, and to characterize the unintentional discrepancies (UD) in their pharmacotherapy in a Brazilian teaching hospital.

MATERIALS AND METHODS

Design and study duration

This cross-sectional study was conducted from 1 April to 17 July, 2013. Additionally, this short report is a secondary analysis of a previous case-control study in process to be published.

Study location

This study was conducted in the surgical, medical and pediatric wards of the University Hospital of the Federal University of Sergipe, in Sergipe, Brazil. The hospital is fully integrated into the Brazilian Unified Health System (SUS) and has 123 beds divided into paediatric, psychiatric, surgery, internal medicine and intensive care wards.

Study sample and patient selection

The recommended sample size calculated for this study was 325 patients, in accordance with Moser and Kalton (1985). The inclusion criteria were hospitalization for longer than 24 h from Monday to Friday. For children, patients, family or caregiver was asked to authorize their inclusion in the study. Patients who were excluded when their medical records were not available at the time of evaluation and interview was not possible to be conducted. In the hospital, there were no admissions on weekends and no MR practices being developed.

The process of obtaining the best possible medication history (BPMH)

In the hospital, the admissions are planned and performed only in the morning, and there are no admissions on weekends. At admission, each patient was evaluated by a physician (or evaluated by a medical student and further evaluated by a physician) or resident physician. All evaluations were written and stored in the clinical records, as well as descriptions of the physicians’ interventions, requests for tests, and evaluations from other professionals. In some of the evaluations, the cooperation of parents and/or caregivers was necessary to assess relevant information. It is important to highlight that there are no medication reconciliation practices standardized in the hospital. Before the study begin, the pharmacist-researcher responsible for the collection and evaluation of data conducted a pilot study on March, 2013, to familiarize herself with the process of hospital admission, calibrate the medication use record, and improve the data collection method.

A structured questionnaire developed by the researchers and adapted from the literature was used to collect data at four steps (Gleason et al., 2004; Cornish et al., 2005; Coffey et al., 2009; Giménez-Manzorro et al., 2011). At step 1, the pharmacist-researcher collected data from the admission records, which were available at hospital admission and generated whenever patients were admitted. The records included sociodemographic information, the ward in which the patient was admitted, and the reason for hospitalization. At step 2, the pharmacist-researcher recorded the first prescription made by the physician responsible for admission. At step 3, the patient's medical record was reviewed to obtain the pharmacotherapy history as recorded by the physician based on the following data: patient’s main complaints, history of previous diseases, questions on previous medications and allergies, and the conduct of the physician responsible for admission.

At step 4, a clinical interview was performed with the patient and/or their caregiver. The following variables were analyzed: way to acquire medication, allergies (to medicines, foods, and other), alerts and special needs, habits and addictions, and medications that were being used prior to admission. Medications that the patient used sporadically, supplements, vitamins, and those whose names the patients and/or caregivers could not recall were excluded.

To obtain higher accuracy of data, all sources of information available at the time of interview were evaluated. This included the interview with the caregiver, the patient records, and data on hospital transfer (for cases in which the patient was shifted from another hospital). The prescription medication taken by the patient was also investigated. The time spent at each of the four assessment steps was recorded. All evaluations occurred until 36 h after admission. After collection, the pharmacist-researcher and three pharmacy students analyzed the data collected and assessed if there were any unintentional discrepancies. In the case of divergences, a second researcher analyzed the data.

This study defined unintentional discrepancies (UD) as the unjustified variations between the patients’ previous medication use history and the pharmacotherapy prescribed during hospitalization. These UD were classified as medication omissions (when it occurs an omission of a required medication), differences in dosage or in the frequency of administration, therapeutic duplications and initiation of therapy without justification (Gleason et al., 2004; Cornish et al., 2005; Coffey et al., 2009; Giménez-Manzorro et al., 2011; Magalhães et al., 2014). The same method to acquire the BPMH was used in a case-control study in process to be published.

Statistical analysis and ethical considerations

The Epinfo statistical program was used to examine associations
RESULTS

In this study, 358 patients were included. In total, 327 UD were found in 150 patients (41.90%). Regarding to the types of UD, omission was the most prevalent (n = 128, 85.33%), followed by different doses (n = 20, 13.34%), erroneous frequency (n = 1, 0.66%), and unjustified start of treatment (n = 1, 0.66%). Of all patients included in the study, 261 (72.90%) were adults with 151 women. The mean age was 47.16 ± 18.80 (14 to 93) years. No statistically significant association was found between the presence of UD and type of patient: child or adult (χ² = 0.771, p = 0.380), gender (χ² = 1.217, p = 0.269), and the patients’ age (χ² = 9.119, p = 0.104). At admission documentation, there was no record of previous pharmacotherapy in 117 adult patients (44.82%; 95% CI: 0.44 to 0.45), and 137 of them (52.49%; 95% CI: 0.52 to 0.53) were not questioned about their allergies. Similarly, 52 children (53.60%; 95% CI: 0.53 to 0.54) had no record of previous medication history reported in their medical records. There was also no record of allergies for 72 children (74.22%; 95% CI: 0.73 to 0.74). A statistically significant association was found between the presence of UD and the questions concerning previous medication (χ² = 6.422, p = 0.011), but not with the questions regarding allergies (χ² = 1.393, p = 0.237). Another variable observed was that 112 patients (31.28%; 95% CI: 0.26 to 0.36) brought the drugs they used at home to the hospital. A statistically significant association (χ² = 39.121, p = 0.001) between this variable and the presence of UD was found. Regarding to time evaluation, the analysis of medical records was the step that proved to be most time-consuming in the assessment of the pharmacotherapy history. Table 1 shows the average, the minimum, and the maximum time for each evaluation point. A statistically significant association was found between the presence of UD and the total time spent on the review of the pharmacotherapy history (χ² = 13.177, p = 0.001).

DISCUSSION

One association found in this study suggests that the review of the pharmacotherapy history demanded more time during the investigation of discrepancies. This amount of time was different from the time reported in other studies (Gleason et al., 2004; Stone et al., 2010). This may be due to methodological differences, as well as differences in the sources of information used to obtain the pharmacotherapy histories. The incomplete or inaccurate acquisition of the pharmacotherapy history as well as omission of important information (for example, drug-drug interactions and allergies) can cause risk to the patients during hospitalization as an indicator for inappropriate medications (Nester and Hale, 2002; Mueller et al., 2012). In this context, the pharmacist can complement the interview carried out by the physician during MR and to increase patient safety (Curatolo et al., 2014).

The unintentional discrepancies may occur when there are no questions regarding the patient’s medication history or no recording of the data obtained on the use of medications prior to admission. The lack of medical questioning about previously medications used may have been a major cause of medication omission in this study.

Stephens and colleagues claim that the failure to record allergies occurs more frequently and may increase when documented with acronyms and summary information (Stephens et al., 2008). Thus, improving the interviews with patients and caregivers as well as the documentation of medical records can be decisive in reducing patients’ allergic reactions, especially in children.

Regarding the use of medications prior to hospital admission, Nayar and Kozakiewicz (2013) reported that sometimes patients are benefited by the continued use of their pharmacotherapy, thus, reducing the risks of treatment discontinuation. Moreover, such an initiative can reduce the patients’ medication costs to the hospital. Nevertheless, it is indispensable keeping in view clinical condition of the patient to evaluate the treatment. The association found may indicate that the lack of reassessment of these drugs in the wards may be related to the presence of discrepancies.

This study has strengths and limitations. Strengths of the present study include: addition of children and adult patients, observation of the presence of allergies noted in the medical records, and structured interviews with the patient and/or their caregiver. Limitations include: no investigation of the clinical relevance of the discrepancies found, reflection of the characteristics of the study location in...
the data collected, and absence of integrated information system on the pharmacotherapy of patients in Brazil (for example, health system database or data from community pharmacies).

Conclusion

In summary, the present study revealed the prevalence of UD in the studied hospital emphasizing the importance of implementation MR processes. Moreover, this paper points out that the assessment of the history of medications used is a complex practice, in which the pharmacist can be an ally.

Conflict of Interests

The authors have not declared any conflict of interest.

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REFERENCES


Review

Difficulties in antifungal therapy with amphotericin B and the continuous search for new formulations: A literature review

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Despite advances in the research on new antifungal agents, Amphotericin B (AmB) is still considered as the antifungal of choice for treating most systemic mycoses due to its potency and broad-spectrum action. However, this drug has limited use because of its toxic effects on kidneys, liver and blood. The search for new and safe formulations of AmB is essential because of the emergence of antifungal resistance to other drugs and the increased number of immunosuppressed patients. Nanoparticles are a promising alternative towards achieving lower toxicity and improved pharmacokinetic properties. This study is a literature review of the use of AmB and the toxicity of formulations. Some of the current new formulations show some advantageous characteristics as compared to AmB. However, there is still need for a continued search for an effectively improved formulation.

Key words: Amphotericin B, toxicity, nanotechnology, pharmaceutical technology.

INTRODUCTION

Systemic fungal infections lead to high morbidity and mortality, particularly in patients with weakened immune systems, such as HIV patients, transplant recipients and/or those with hematologic disorders, and those treated with corticosteroids and/or chemotherapy (Chattopadhyay and Jafurulla 2011; Finquelievich et al., 2011). Amphotericin B (AmB) is a polyene macrolide antibiotic with antifungal activity, mainly used for systemic infections (1). The therapeutic benefits of this drug and its analogs are also being studied in vitro in prion disease (Soler et al., 2008).

In this case, the mechanism of action is speculated as the production of neurotrophic factors in the microglia, but...
it has not been clearly elucidated (Motoyoshi et al., 2009). Another suggestion is that amphotericin B may interfere with prion spread. However, further studies are required (Demainay et al., 1997).

In addition to studies on prion diseases, AmB has already been defined as a broad spectrum antifungal, effective against almost all species of Candida spp., some species of Aspergillus spp., Cryptococcus neoformans, Mucor spp., Sporothrix schenckii, Blastomyces dermatitidis, Coccidioides immitis, Histoplasma capsulatum, Paracoccidioides brasiliensis and Penicillium marneffei (Miceli and Chandrasekar 2012; Ellis, 2002).

However, although AmB is a broad spectrum antibiotic, it has a great impact on homeostasis, depleting the functioning of renal and hepatic systems, and causing hematoletic alterations because the drug exhibits affinity to cholesterol (Brajtburg et al., 1990).

Thus, this article aims to gather information on AmB mechanism of action and toxicity and to evaluate the most recent alternative formulations that show increased control of undesirable effects.

MATERIALS AND METHODS

This study employed an integrative literature review using articles on the mechanism of action, toxicity and alternative formulations related to AmB, published between 1980 and 2012 and indexed in the PubMed, Scielo and ScienceDirect databases.

LITERATURE REVIEW

Structural, pharmacological, and physical and chemicals aspects of Amphotericin B

The drug was first isolated in 1955 from the bacterium Streptomyces nodosus (Chattopadhyay and Jafurulla, 2011). The molecular structure contains 37 carbon atoms with a hydrophobic portion and a sequence of seven conjugated double bonds with lipophilic characteristic containing polar substituents, especially hydroxyls (Figure 1). The structure of AmB clearly shows the basis of the drug’s name, that is, amphoteric physical and chemical characteristics. The molecule is about 24 Å in length, which is equivalent to a half phospholipid layer (Lemke et al., 2005).

The drug’s mechanism of action has not been fully clarified. However, the current and most accepted hypothesis cites that amphotericin interacts with all sterols. However, it has a greater affinity for ergosterol, which forms part of the fungal membrane, than with human cholesterol. The drug-membrane interaction disrupts phospholipids in the fungal membrane, creating channels that allow the influx of ions and molecules and result in an ionic imbalance and likely cell death (Figure 2) (Brajtburg et al., 1990; Yano et al., 2009).

The interaction between Amphotericin B molecules with cell membrane components indicates two possible mechanisms for the formation of membrane pores. Gray and colleagues (2012) describe the formation of these pores in detail and contribute to the understanding of the structure-activity relationships of new analogs of this reference drug (Gray et al., 2012). Side chains C [micosamina] and D [hydroxyl] (Figure 2) are indicated as pharmacophoric groups of AmB, that is, essential for the pharmacological response of the two proposed mechanisms.

The activation of the Na+/K+ ATPase pump occurs due to the high sodium intake and potassium and magnesium output through the pores. Mitochondrial respiration is intensified and the consumption of oxygen increased to maintain the intracellular ATP levels. Energy depletion, free radical formation and accumulation of intracellular calcium occur when the demand exceeds ATP production capacity. All these processes could lead to lethal damage to cells through apoptosis and necrosis (White et al., 1998).
Figure 2. Mechanism of action of Amphotericin B on fungal cell membrane with consequent opening of hydrophilic pores. The electrostatic interaction (hydrogen bonding) between mycosamine and ergosterol hydroxyls can be observed. Phospholipids (A), ergosterol (B), the mycosamine (C) and hydroxyl (D) pharmacophore groups are highlighted.

In addition, several studies have demonstrated the involvement of oxidative stress in the antifungal activity of AmB, especially in *C. albicans*. The generation of reactive oxygen species and hydroxyl radicals promoted by the drug leads to damage in the fungal cell through protein oxidation, peroxidation of membrane lipids, or cleavage of DNA or RNA (An et al., 2009; Okamoto et al., 2004). This theory is supported by studies demonstrating decreased AmB activity in hypoxic conditions (Warn et al., 2004) enhanced cell damage and in vitro inhibition of hemolysis are observed in the presence of pro-oxidants and catalase, respectively (Brajtburg et al., 1990).

Understanding of the pharmacological and pharmacokinetic properties of AmB, such as maximum activity in the pH range from 6.0 to 7.5 with inactivation at low pH and light sensitivity, is essential for control of its biological effects. The pharmacological effect may have both fungicide and fungistatic characteristics, depending on not only the blood and/or tissue concentration achieved, but also the sensitivity or resistance of the microorganism (Vartivarian et al., 1993). However, a major limitation in the use of AmB includes low drug solubility in most aqueous solvents and solubility in dimethylsulfoxide, dimethylformamide, and propylene glycol (Filippin and Souza, 2006).

Moreover, because it is insoluble in water, it is presented in association with deoxycholate detergent in phosphate buffer (Filippin and Souza, 2006); this system is not homogeneous, and may have three different (polymorphic) forms: monomeric, oligomeric and aggregates of AmB mixed with deoxycholate pure micelles. A quantitative balance is observed between the forms: the aggregate form is related to the highest toxicity (Lamy-Freund et al., 1991; Legrand et al., 1992). The current formulation of AmB (Fungizone®) contains sodium deoxycholate, a surfactant agent needed to promote AmB micellization (Silveira et al., 2013).

Administration of AmB is almost exclusively intravenous because it shows very low gastrointestinal absorption. The drug, diluted in a glucose solution, is commonly infused at a dose of 0.5 mg/kg and a concentration of 0.1 mg/ml, infusion time ranges from two to four hours (Patel, 1998). Infusion time determines administration in hospital environments: prolonged venous access increases costs as well as the risk of secondary infections, especially in immunocompromised patients (Brajtburg et al., 1990; Leon et al., 2011; Sivak et al., 2011).

Deoxycholate readily separates from AmB when administered intravenously. AmB molecules...
subsequently bind to plasma lipoproteins (above 95%) (Lewis and Wiederhold, 2003), initially binding to HDL and subsequently to LDL through the action of the cholesteryl ester transfer protein or lipoprotein lipid transfer protein (Hamill, 2013).

Most of the drug leave the systemic circulation and is transported to the liver and other organs. AmB concentrations in inflamed areas such as the peritoneum, pleura, and joints are approximately two-thirds of those in the serum. AmB only slightly penetrates the meninges, brain, saliva, bronchial secretions, vitreous humor, amniotic fluid, muscles, and bones in their normal or inflamed states (Hamill, 2013). Approximately, 20-30% of AmB is metabolized in the liver and excreted in bile in the feces. About 2-5% of AmB found in the urine was not metabolized and remains biologically active (Bekersky et al., 2002). Bekersky and colleagues (2002) found that up to two-thirds of d-AmB is excreted unchanged in urine (20.6%) and feces (42.5%), suggesting that there is no extensive metabolism of the drug (Andes, 2006).

Existing studies classify polyenes - AmB - as concentration-dependent compounds (Groll et al., 2000). However, these studies show conflicting results such as the observation of similar antifungal action in the early hours or persistence after 24 h of administration, which may reflect a slow diffusion in vivo in tissues. Although it is established that AmB has a clear concentration-dependent activity (Groll et al., 2000), there is probably a free fraction ceiling effect (bioactive) based on plasma protein binding and solubility, which could vary according to the site of infection in organs such as kidneys, lungs, liver and brain (Wiederhold et al., 2006).

The pharmacokinetic objective of any antifungal treatment is to achieve therapeutic concentrations at the infection site. Thus, in addition to the drug, the type of fungus causing the infection and the infection site must be considered. Most pathogenic fungi lie in the extracellular medium; therefore, the serum concentration would be a reliable marker for appropriate therapy. However, in compartmentalized infections in the central nervous system, such as cryptococcal meningoencephalitis, the concentration in the brain parenchyma can be more important than it is in infection sites which cause cell lysis (Huang et al., 2002; Cybulskia et al., 1984). Other authors have also shown the interaction between AmB and the membrane of polymorphonuclear leukocytes (Marzullo et al., 1997; Boggs et al., 1991) and described the important modulatory effects, such as inhibition of chemotaxis and decreased the production of antibodies, of this drug on these cells (Lewis et al., 2005; Burgess et al., 2000). AmB presents low therapeutic index. Therefore, even infusion at therapeutic doses causes serious acute adverse reactions (fever, chills, nausea, vomiting, headache and even cardiac arrhythmias, seizures, and liver failure) (Yano et al., 2009; Klepser, 2011; Laniado-Laborin and Cabrales-Vargas, 2009; Louie et al., 1994; Arning et al., 1995). It is believed that this reaction occurs in the use of the deoxycholate formulation resulting from activation of cytokines’ cascade including the secretion of the tumor necrosis factor by activated macrophages (Jung et al., 2009; Burgess et al., 2010). The effects caused by drug toxicity can be anemia, leukopenia, thrombocytopenia, and nephrotoxicity (Patel, 1998).

Numerous attempts to reduce the toxicity of AmB are found in recent years. Among them are the development of new formulations such as liposome base encapsulation (AmBisome), the formation of lipid complexes (ABELCET®), colloidal dispersions (Amphocil®) and nanoparticles. These new formulations have demonstrated decreased toxicity and increased therapeutic efficacy; however, their high cost has limited their use (Filippin and Souza, 2006; Iman et al., 2011; Kleinberg,
The liposomal formulation is the drug encapsulation into unilamellar liposomes aimed at decreasing the drug's affinity for mammalian cells and consequently its toxicity, and increasing its residence time in the bloodstream, consequently increasing the plasma concentration by reducing redistribution and renal excretion (Walsh et al., 2001; Laing et al., 1994). The drug concentration increases in the liver with the fall of the plasma concentration. The formulation shows lower nephrotoxicity as compared to AmB deoxycholate, allowing its use at high doses (Cesaro et al., 1999). However, anaphylactic reactions, which were less frequent than with the use of AmB deoxycholate, occurred with its use (White et al., 1998; Sundar et al., 2010; Janknegt et al., 1992). Anaphylactic reactions are mediated by the release of histamine and are reactions with an allergic character (Cesaro et al., 1999). Sundar and colleagues (2010) conducted a study comparing toxicity related to the infusion of the deoxycholate and liposomal formulations (Kleinberg, 2006), and observed that the infusion-related toxicity in the liposomal formulation was 24% lower than in the deoxycholate formulation (Walsh et al., 1998).

It is believed that the liver serves as an AmB reservoir (Walsh et al., 1992). Liver macrophages contain a lipid complex, a large structure with the capacity to rapidly absorb and gradually release AmB, resulting in lower concentrations in the bloodstream and kidneys. When compared with deoxycholate AmB, the liposomal formulation maintained drug efficacy, showed lower toxicity and lower serum creatinine values and no changes in electrolytes and liver enzymes; increased bilirubin was observed (Bekersky et al., 1999; Bowden et al., 2002). The colloidal dispersion composed of AmB and sodium cholesteryl sulfate forms a dispersion of disk-shaped particles which prevents the transfer of AmB to mammalian cells. The absence of contact with mammalian cells reduces AmB toxicity because the colloidal particles do not bind to plasma proteins or blood cells and show low affinity with cholesterol (Klepser, 2011). However, this formulation showed more side effects in relation to infusion reactions, such as chills and fever, hypotension, nausea and tachycardia, than the deoxycholate AmB formulation (Manandhar et al., 2008; Mora-Duarte et al., 2002).

New AmB formulations have been studied to reduce the toxicity of this drug. Nanoparticles formulations, for example, are recognized as foreign bodies by the immune system; they are engulfed by macrophages and later released, reducing systemic side effects (Harbarth et al., 2001).

**Chronic side effects nephrotoxicity**

Nephrotoxicity represents the greatest impasse in the use of AmB because of its high incidence and morbidity. The use of this drug leads to some degree of renal dysfunction, which varies in severity from one patient to another with a distinctly dose-dependent effect. The comparison between the conventional formulation with the AmB colloidal dispersion formulation showed an incidence of renal toxicity ranging from 25 to 49%. The serum creatinine levels observed in these patients were within an average increase of 1.5 to 2 times the normal range (Manandhar et al., 2008). A rate of 24.8% renal toxicity was demonstrated in patients in another study using doses of 0.6 to 1 mg/kg of amphotericin B deoxycholate (Shigemi et al., 2011). The elevation of this renal marker, reaching up to three times the upper normal limit, was also observed by other authors (Cesaro et al., 1999; Shigemi et al., 2011).

Nephrotoxicity (28%) and an increase of 50-100% in serum creatinine (Patel et al., 2011) was observed in a study of 494 patients using conventional AmB, data similar to that reported by Patel (2011), and demonstrating dose and time dependence effects. The testing of the liposomal formulation in a retrospective analysis of 22 patients showed a similar result in which 27.3% of patients presented renal effects (Odabasi et al., 2009). Therefore, according to these two papers, there was no significant difference in renal toxicity between the conventional and liposomal preparations. However, other studies found greater harmful variations with the use of liposomal AmB, with 56% showing nephrotoxicity (Bagnis and Deray, 2002) and up to 100% increase in serum creatinine (Cesaro et al., 1999). Renal side effects are common with the use of AmB in both conventional and liposomal formulations. Further robust studies are needed to confirm these results and accurately minimize result variation between studies.

The mechanism that generates toxicity is associated with dysfunction in the renal blood flow resulting in the direct structural lesion in tubule cells, reduction in glomerular filtration rate and, consequently, electrolyte disturbances and acid-base imbalance (Mayer et al., 2002). Thus, the main manifestations of nephrotoxicity are a reduction of glomerular filtration and hypokalemia and hypomagnesemia caused by direct tubular lesion; nephrocalcinosis and renal tubular acidosis might also occur (Klepser, 2011; Longuet et al., 1991).

Renal hypoperfusion with a decrease in urine production occurs minutes after drug administration, even if the systemic blood pressure is unchanged. The medullary portion of the kidney is poorly irrigated, suffering from this hypoperfusion. Eventually, nephron function is impaired especially in patients who are treated with a high AmB dose for a long period (Klepser, 2011). This impaired function can lead to polyuria, polydipsia, decreased creatinine clearance and increased creatinine in the serum, increase in sodium and potassium excretion in the urine, and kidney tubule damage due to difficulty in concentrating urine (Wasan et al., 1990; Fisher et al., 2001; Hillery, 1997; Bekersky et al., 2002).
and decrease in renal blood flow resulting in vascular congestion due to tissue hypoxia followed by ischemia. Moreover, the ischemic process activates inflammatory mediators, such as TNF-α and interleukin-1 cytokines, in addition to superoxide anions, which stimulate thrombogenic events through the oxidation of low-density lipoproteins (Holler et al., 2004).

Renal alterations are of particular concern in patients with previous kidney lesions or those who had received a kidney transplant, and when the patient concomitantly uses other nephrotoxic agents such as aminoglycoside antibiotics (Brajtburg et al., 1990). The risk of nephrotoxicity increases with the simultaneous use of diuretics (Shigemi et al., 2011). Massive rehydration and electrolyte correction are among the means used to prevent nephrotoxic effects (Brajtburg et al., 1990; Inselmann et al., 2002).

Nephrotoxicity is a multifactorial effect (Bagnis and Deray, 2002). Studies show that this effect is closely related to the patient's condition and concomitant use of nephrotoxic agents. Therefore, the patient must be monitored to reduce the risks of renal toxicity and consequent treatment discontinuation.

Hepatotoxicity

AmB may also cause alterations in the liver. The risk of liver toxicity is observed by the increase in liver enzymes (aspartate and alanine aminotransferases, and alkaline phosphatase) and bilirubin (Moribe et al., 2010). Other typical signs of liver damage can be observed, such as the reduction of phagocytic activity in Kupffer cells and vacuolation of hepatocytes. The use of conventional AmB resulted in greater alterations in the liver than the use of the liposomal formulation. However, such effects may be more related to the vehicle used, which in this case was deoxycholate (Amaral et al., 2009).

Patel and colleagues (2011) investigated 75 patients using the AmB liposomal formulation. Biochemical tests showed that 21% presented hepatotoxicity based on the bilirubin criterion of above 1.5 mg/dl and three times above normal levels of aspartate aminotransferase (AST) or glutamic-oxaloacetic transaminase (AST), and alanine aminotransferase (ALT) or glutamic pyruvic transaminase (GPT) (Bagnis and Deray, 2002).

Moribe (2010) compared the use of AmB nanoparticles with the conventional formulation in mice at an intravenous dose of 1 and 2 mg/kg and observed that the nanoparticle formulation did not cause significant alterations in the alanine aminotransferase level when compared with conventional AmB. AST increased up to 300 IU/L at the dose of 2 mg/kg; it did not exceed 200 IU/L with the use of nanoparticles (Mayer et al., 2002). Amaral (2009) obtained similar results using deoxycholate AmB and nanoparticles in mice: no alterations were observed in the ALT and AST enzymes using the dose of 2.7 mg/kg/day of Amphotericin in nanoparticles at one dose higher than the tolerable limit (Souza and Campa, 1999). This result may have resulted from the slow and steady release through the nanocarrier. Studies show that the nanoparticles AmB formulation is safer than other types of formulations; however, new experiments need to be conducted in humans for a better understanding of the mechanism of action and achievement of improved results on safety.

Hematotoxicity

AmB also causes hematological alterations such as anemia and thrombocytopenia (Walsh et al., 1992). Anemia results from the suppression of erythropoiesis but not of hemolysis: the latter usually occurs in vitro and when high doses of the drug are used (Arning et al., 1995).

A retrospective study of 22 patients using the liposomal AmB formulation decreased the concentration of hemoglobin and dose-dependent anemia and thrombocytopenia in patients; 50% of patients became likely to develop anemia and thrombocytopenia when using the doses of 3 and 3.3 mg/kg, respectively. Thrombocytopenia occurred in 57.9% of patients, thus confirming the hematological damage caused by such therapy (Odabasi et al., 2009).

The comparison between one AmB liposomal emulsion and the conventional formulation in vitro showed that the conventional formulation is more hemolytic than the liposomal. However, hemolysis decreases if the solution is heated due to a change in the drug's aggregation state (Darole et al., 2008). The concentration of the liposomal formulation needs to be fifteen times higher than the conventional formulation to cause the same inflow of potassium in human blood cells, which leads to cellular damage (Sheikh et al., 2010). An in vitro study comparing the microemulsion AmB to deoxycholate AmB formulations in human blood cells demonstrated that the encapsulation significantly reduces hemolysis. The conventional AmB presented 100% hemolysis at the concentration of 5 μL/ml while the other formulation presented approximately 10% (Nahar et al., 2008); the nanoparticles presented less than 1% hemolysis at the concentration of 200 μL/mL (Xu et al., 2011).

An experiment with mice using the conventional and liposomal AmB formulations and nanoparticles at the doses of 1, 5, and 10 mg/kg showed that the conventional formulation caused significant decrease in hemoglobin, hematocrit and platelet counts; these alterations were not observed with the use of nanoparticles and the liposomal formulation, except for platelet counts in which there was a significant decrease in all groups and which could not be explained in that study (Krog-Hansen et al., 2006). In that study, the use of nanoparticles did not cause hemolysis in vitro. Another study observed that the
encapsulation of AmB reduced the hematological effects when compared with the use of conventional AmB; reduction in platelet count was not observed with the use of nanoparticles (Sterling and Merz, 1998).

**Resistance**

Another limiting factor in the treatment of fungal infections is the emergence of drug resistance in fungi. Although rare, resistance to AmB has been described, especially in non-*C. albicans* species. Some species such as *Candida lusitaniae* and *Candida guilliermondii* possess intrinsic resistance to AmB (Dalazen et al., 2011; Krogh-Madsen et al., 2006a). Dalazen and coworkers (2011) demonstrated a high rate of AmB resistance (96.6%) in clinical isolates from elderly patients with oral erythematous candidiasis. Resistance is associated with alterations in the composition of the fungal cell lipid membrane and increase or decrease of ergosterol. *C. albicans* isolates were considered resistant to AmB when presented the minimum inhibitory concentration above 2 mg/ml in *in vitro* antifungal susceptibility testing (Souza and Campa, 1999). Some species, such as *C. lusitaniae* and *C. guilliermondii*, may have intrinsic resistance to AmB (Krogh-Madsen et al., 2006b; Colombo et al., 2006; Antunes et al., 2004).

In Brazil, studies conducted to identify which *Candida* spp. would present resistance to AmB did not identify resistant strains (Wayne, 2002; Negri et al., 2010; Mukherjee et al., 2010). Negri et al. (2010), observed that AmB showed the lowest MIC against *C. albicans* among all the tested drugs (fluconazole, itraconazole, voriconazole and AmB).

**Conflict of Interests**

The authors have not declared any conflict of interests.

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Related Journals Published by Academic Journals

- Journal of Medicinal Plant Research
- African Journal of Pharmacy and Pharmacology
- Journal of Dentistry and Oral Hygiene
- International Journal of Nursing and Midwifery
- Journal of Parasitology and Vector Biology
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