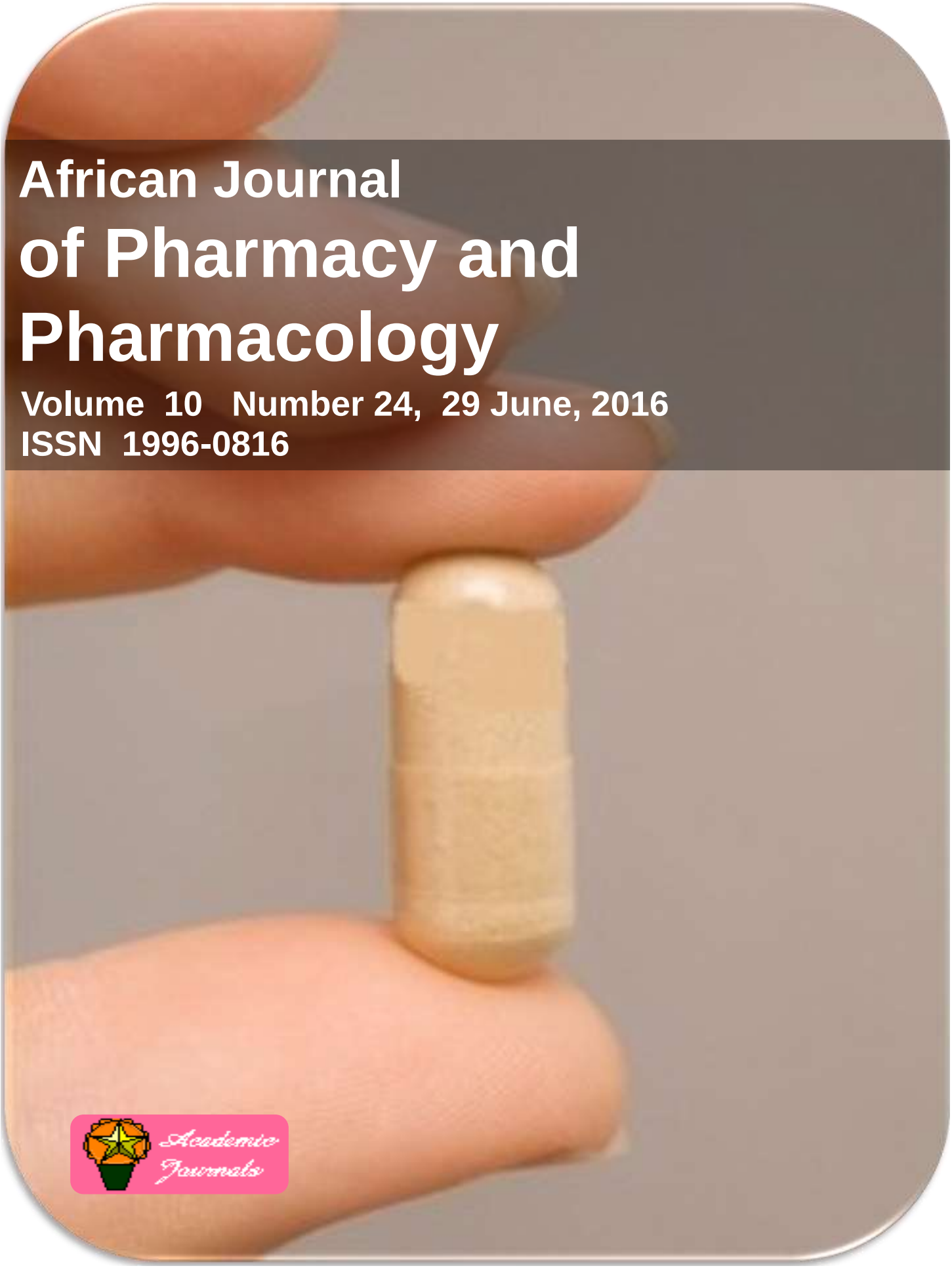

African Journal of Pharmacy and Pharmacology

Volume 10 Number 24, 29 June, 2016
ISSN 1996-0816

Academic Journals

ABOUT AJPP

The **African Journal of Pharmacy and Pharmacology (AJPP)** is published weekly (one volume per year) by Academic Journals.

African Journal of Pharmacy and Pharmacology (AJPP) is an open access journal that provides rapid publication (weekly) of articles in all areas of Pharmaceutical Science such as Pharmaceutical Microbiology, Pharmaceutical Raw Material Science, Formulations, Molecular modeling, Health sector Reforms, Drug Delivery, Pharmacokinetics and Pharmacodynamics, Pharmacognosy, Social and Administrative Pharmacy, Pharmaceutics and Pharmaceutical Microbiology, Herbal Medicines research, Pharmaceutical Raw Materials development/utilization, Novel drug delivery systems, Polymer/Cosmetic Science, Food/Drug Interaction, Herbal drugs evaluation, Physical Pharmaceutics, Medication management, Cosmetic Science, pharmaceuticals, pharmacology, pharmaceutical research etc. The Journal welcomes the submission of manuscripts that meet the general criteria of significance and scientific excellence. Papers will be published shortly after acceptance. All articles published in AJPP are peer-reviewed.

Contact Us

Editorial Office: ajpp@academicjournals.org

Help Desk: helpdesk@academicjournals.org

Website: http://www.academicjournals.org/journal/AJPP

Submit manuscript online http://ms.academicjournals.me/

Editorial Board

African Journal of Pharmacy and Pharmacology

Table of Contents: Volume 10 Number 24 29 June, 2016

ARTICLES

academicJournals

Vol. 10(24), pp. 508-511, 29 June, 2016
DOI: 10.5897/AJPP2016.4588
Article Number: 27EE6F359429
ISSN 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

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

Carina Carvalho Silvestre[1]*, Lincoln Marques Cavalcante Santos[1], Rafaella de Oliveira Santos Silva[1], Genival Araújo dos Santos Júnior[1], Alfredo Dias Oliveira-Filho[1,2], Iza Maria Fraga Lobo[3] and Divaldo Pereira de Lyra Júnior[1]

[1]Laboratory of Teaching and Research in Social Pharmacy (LEPFS), Department of Pharmacy, Federal University of Sergipe, São Cristóvão, SE, Brazil.
[2]School of Nursery and Pharmacy (ESENFAR), Federal University of Alagoas, Maceió, AL, Brazil.
[3]Risk Management, Teaching Hospital of Federal University of Sergipe, Aracaju, SE, Brazil.

Received 3 May, 2016; Accepted 6 June, 2016

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

*Corresponding author. E-mail: farm.carina@gmail.com; lepfs@gmail.com. Tel/Fax: +55 79 988369005.

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 Epiinfo statistical program was used to examine associations

Table 1. Average duration of data collection at the four pre-established steps, Brazil.

Parameter	Step 1*	Step 2*	Step 3*	Step 4*	Total
Average (minutes)	1.68 ± 0.59	2.04 ± 1.52	5.15 ± 3.82	3.78 ± 2.11	12.61 ± 5.54
Range (minutes)	1-7	1-13	1-19	1-19	4-37

*Step 1 – Collection of demographic data and other data from the admission form. *Step 2 – Review of prescription by the physician responsible for admission. *Step 3 – Review of the patient's record. *Step 4 – Clinical interview with the patient and/or their caregiver.

between the data using Chi-square tests with a significance level of 0.05. The study was authorized by the Hospital Board and the Research Ethics Committee of the HU/UFS under CAAE number 08125912.5.0000.0058.

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 (χ^2 = 0.771, p = 0.380), gender (χ^2 = 1.217, p = 0.269), and the patients' age (χ^2 = 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 (χ^2 = 6.422, p = 0.001), but not with the questions regarding allergies (χ^2 = 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 (χ^2 = 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 (χ^2 = 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 pharmacoterapy, 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

ACKNOWLEDGMENTS

We would like to thank all employees of the hospital for the support on the development of the present study. Sincere gratitude to the Coordination for the Improvement of Higher Education Personnel (CAPES) for the funding.

REFERENCES

Bell CM, Brener SS, Gunraj N, Huo C, Bierman AS, Scales DC, Bajcar J, Zwarenstein M, Urbach DR (2011). Association of ICU or hospital admission with unintentional discontinuation of medications for chronic diseases. JAMA 306(8):840-847.

Coffey M, Mack L, Streitenberger K, Bishara T, de Faveri L, Matlow A (2009). Prevalence and Clinical Significance of Medication Discrepancies at Pediatric Hospital Admission. Acad. Pediatr. 9(5):360-365.

Cornish PL, Knowles SR, Marchesano R, Tam V, Shadowitz S, Juurlink DN, Etchells EE (2005). Unintended medication discrepancies at the time of hospital admission. Arch. Intern. Med. 165(4):424-429.

Curatolo N, Gutermann L, Devaquet N, Roy S, Rieutord A (2014). Reducing medication errors at admission: 3 cycles to implement, improve and sustain medication reconciliation. Int. J. Clin. Pharm. 37(1):113-120.

Giménez-Manzorro Á, Zoni AC, Rodríguez Rieiro C, Durán-García E, TrovatoLópez AN, Pérez Sanz C, Bodas Gutiérrez P, Jiménez Muñoz AB (2011). Developing a programme for medication reconciliation at the time of admission into hospital. Int. J. Clin. Pharm. 33(4):603-609.

Gleason KM, Groszek JM, Sullivan C, Rooney D, Barnard C, Noskin GA (2004). Reconciliation of discrepancies in medication histories and admission orders of newly hospitalized patients. Am. J. Health Syst. Pharm. 61(16):1689-1695.

Kwan JL, Lo L, Sampson M, Shojania KG (2013). Medication reconciliation during transitions of care as a patient safety strategy: A systematic review. Ann. Intern. Med. 158:5(Part 2):397-403.

Magalhães GF, Santos GN, Rosa MB, Noblat LA (2014). Medication reconciliation in patients hospitalized in a cardiology unit. PLoS One. 9(12):e115491.

Moser CA, Kalton G (1985). Survey methods in social investigation. Gower Publishing Company Limited, Hants.

Mueller SK, Sponsler KC, Kripalani S, Schnipper JL (2012). Hospital-based medication reconciliation practices: A systematic review. Arch. Intern. Med. 172(14):1057-1069.

Nayar AK, Kozakiewicz J (2013). Storage of patients' home medications during hospitalizations. Am. J. Health Syst. Pharm. 70(7):574-575.

Nester TM, Hale LS (2002). Effectiveness of a pharmacist-acquired medication history in promoting patient safety. Am. J. Health Syst. Pharm. 59(22):2221-2225.

Pevnick JM, Shane R, Schnipper JL (2016). The problem with medication reconciliation. BMJ Qual. Saf. 0:1-5.

Stephens M, Fox B, Kukulka G, Bellamy J (2008). Medication, allergy, and adverse drug event discrepancies in ambulatory care. J. Fam. Med. 40(2):107-110.

Stone BL, Boehme S, Mundorff MB, Maloney CG, Srivastava R (2010). Hospital admission medication reconciliation in medically complex children: An observational study. Arch. Dis. Child. 95(4):250-255.

Zed PJ (2015). Medication reconciliation: more than just a best possible medication history. Can J. Hosp. Pharm. 68(1):4-5.

academicJournals

Vol. 10(24), pp. 512-520, 29 June, 2016
DOI: 10.5897/AJPP2015.4280
Article Number: 2B8BE7059431
ISSN 1996-0816

http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Review

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

Ketllyn S. Voncik[1], Bárbara L. Fermino[2], Nathália C. S. Cardoso[2], Raissa H. de Mattos[2], Eliz C. P. Pinto[2], Jheneffer D. Ignachewski[2], Emerson Carraro[2], Guilherme B. L. de Freitas[2], Weber C. F. N.da Silva[2] and Juliana S. Bonini[2]*

[1]Health Sciences Sector, Graduate Program in Pharmaceutical Sciences, Midwest State University (UNICENTRO), Guarapuava, PR, Brazil.
[2]Health Sciences Sector, Department of Pharmacy. Midwest State University (UNICENTRO), Guarapuava, PR, Brazil.

Received 21 January, 2015; Accepted 18 February, 2016

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

*Corresponding author. E-mail: juliana.bonini@gmail.com, Phone/Fax: 55 (42) 36298137 fax: (43) 34786005.

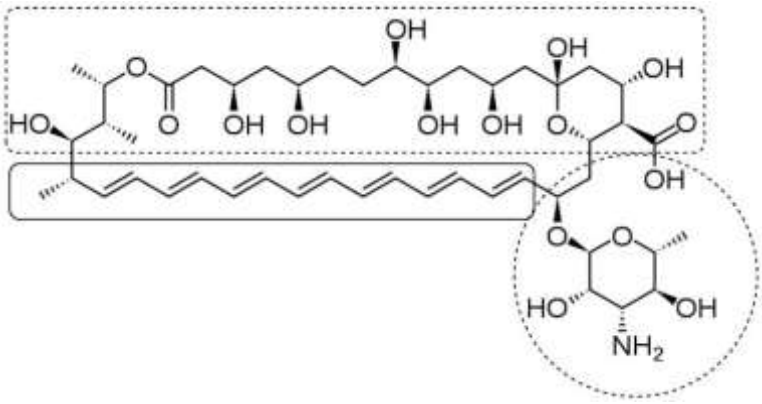

Figure 1. Structural representation of AmB highlighting the pharmacophore hydrophilic (dotted line) and lipophilic (solid line) groups.

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 (Demaimay 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 braziliensie* 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 hematologic 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).

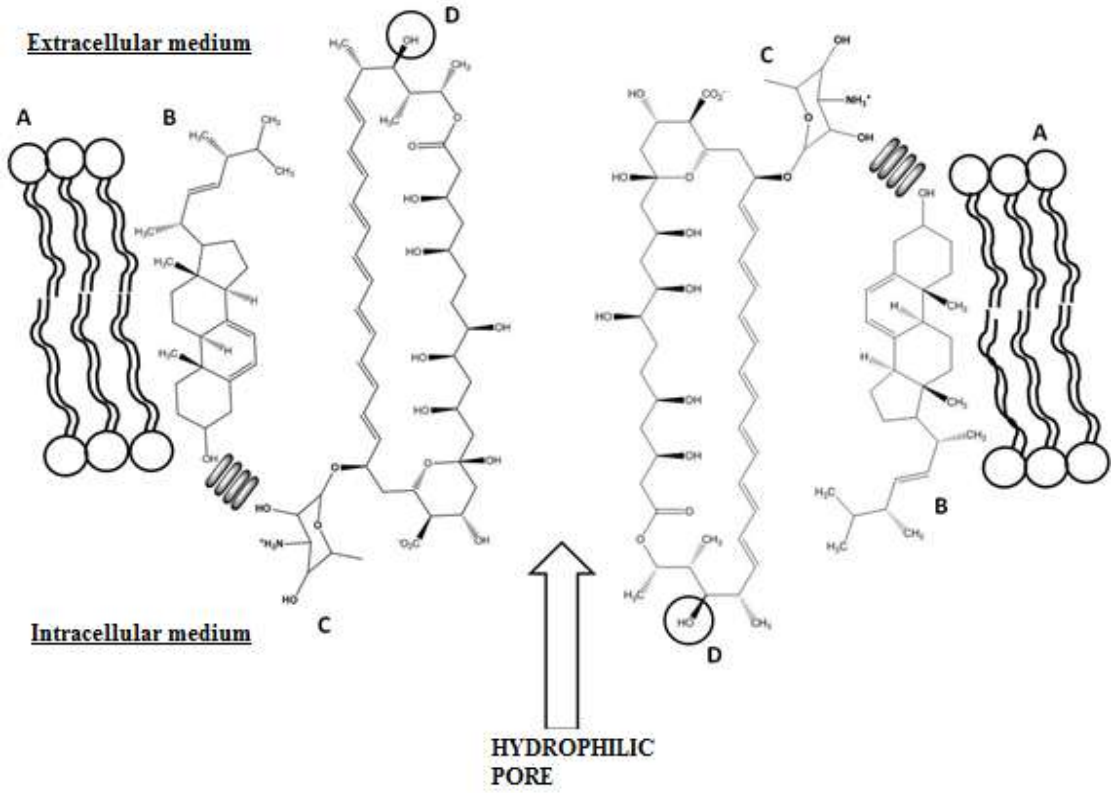

Figure 2. Mechanism of action of Amphotericin B on fungal cell membrane with consequent opening of hydrophilic pores. The electrostatic interaction (hydrogen bonding) between mycosamine and ergosterol hydroxyls can be observed. Phospholipids (A), ergosterol (B), the mycosamine (C) and hydroxyl (D) pharmacophore 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 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 metabolization 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 meningo-encephalitis, the concentration in the brain parenchyma can be more important than it is in infection sites which are easily accessed by the drug. Studies in animals have demonstrated comparable d-AmB penetration into the brain parenchyma in relation to other AmB formulations (Andes, 2006; Lewis et al., 2005).

In fact, treatment with d-AmB (1 mg/kg/day) and L-AmB (5 mg/kg/day) showed the highest peak plasma concentrations (Cmax) and area under the curve (AUC) as compared to treatment with other AmB formulations (ABCD and ABLC). The d-AmB and L-AmB formulations also showed increased antifungal effectiveness (Lewis et al., 2005).

Pharmacodynamic studies showed that d-AmB exhibits species-specific and concentration-dependent activity with 50% effective concentrations (EC50) ranging from 0.10 to 0.12 g/ml for *Aspergillus fumigatus*; 0.36 to 0.53 mg/ml for *Aspergillus terreus*; 0.27 and ≥ 32 mg/ml for *Fusarium solani*; 0.41 to 0.55 mg/ml for *Fusarium oxysporum*; and 0.97 and 0.65 g/ml for *Scedosporium apiospermum* and *Scedosporium prolificans*, respectively (Burgess et al., 2000; Andes et al., 2001). The optimized AmB activity may be achieved for *Candida albicans* by maximizing the peak concentration ratio of the minimum inhibitory concentration (Cmax/MIC). D-AmB also demonstrated prolonged growth inhibitory activity and dose-dependency even at levels below the MIC (Huang et al., 2002; Brajtburg et al., 1980).

The lipid formulations have been developed to increase the therapeutic index of AmB, allowing the use of high doses in the treatment of infectious conditions. Such structurally diverse formulations differ with respect to pharmacokinetics, tissue concentration, microbiological effect and toxicity.

Challenges of antifungal therapy with Amphotericin B

The fact that AmB shows an affinity for cholesterol largely explains the many toxic effects that are described after drug administration in patients (Huang et al., 2002). *In vitro* studies showed that low levels of AmB increase the permeability of biological membranes while high levels cause cell lysis (Huang et al., 2002; Cybulska et al., 1984). Other authors have also shown the interaction between AmB and the membrane of polymorphonuclear leukocytes (Marzzullo 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,

2006; Hillery, 1997; Bekersky et al., 2002).

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.,

1989) 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 uL/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 (Krogh-Madsen 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 guilliermondi* 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. guilliermondi*, 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.

REFERENCES

Amaral AC, Bocca AL, Ribeiro AM, Nunes J, Peixoto DL, Simioni AR, Primo FL, Lacava ZG, Bentes R, Titze-de-Almeida R (2009). Amphotericin B in poly (lactic-co-glycolic acid)(PLGA) and dimercaptosuccinic acid (DMSA) nanoparticles against paracoccidioidomycosis. J. Antimicrob. Chemother. 63:526-533.

An M, Shen H, Cao Y, Zhang J, Cai Y, Wang R, Jiang Y (2009). Allicin enhances the oxidative damage effect of amphotericin B against Candida albicans. Int. J. Antimicrob. Agents 33:258-263.

Andes D (2006). Pharmacokinetics and pharmacodynamics of antifungals. Infect. Dis. Clin. 20:679-697.

Andes D, Stamsted T, Conklin R (2001). Pharmacodynamics of amphotericin B in a neutropenic-mouse disseminated-candidiasis model. Antimicrob. Agents Chemother. 45:922-926.

Antunes AGV, Pasqualotto AC, Diaz MC, d'Azevedo PA, Severo LC (2004). Candidemia in a Brazilian tertiary care hospital: species distribution and antifungal susceptibility patterns. Revista do Instituto de Medicina Tropical de São Paulo 46:239-241.

Arning M, Kliche K, Heer-Sonderhoff A, Wehmeier A (1995). Infusion-related toxicity of three different amphotericin B formulations and its relation to cytokine plasma levels. Mycoses 38:459-465.

Bagnis CI, Deray G (2002). Amphotericin B nephrotoxicity. Saudi J. Kidney Dis. Transplantation 13:481.

Bekersky I, Fielding RM, Buell D, Lawrence I (1999). Lipid-based amphotericin B formulations: from animals to man. Pharmaceut. Sci. Technol. Today 2:230-236.

Bekersky I, Fielding RM, Dressler DE, Lee JW, Buell DN, Walsh TJ (2002). Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans. Antimicrob. Agents Chemother. 46:828-833.

Bekersky I, Fielding RM, Dressler DE, Lee JW, Buell DN, Walsh TJ (2002). Pharmacokinetics, excretion, and mass balance of liposomal amphotericin B (AmBisome) and amphotericin B deoxycholate in humans. Antimicrob. Agents Chemother. 46:828-833.

Boggs J, Chang N, Goundalkar A (1991). Liposomal amphotericin B inhibits in vitro T-lymphocyte response to antigen. Antimicrob. Agents Chemother. 35:879-885.

Bowden R, Chandrasekar P, White MH, Li X, Pietrelli L, Gurwith M, van Burik J-A, Laverdiere M, Safrin S, Wingard JR (2002). A double-blind, randomized, controlled trial of amphotericin B colloidal dispersion versus amphotericin B for treatment of invasive aspergillosis in immunocompromised patients. Clin. Infect. Dis. 35:359-366.

Brajtburg J, Medoff G, Kobayashi GS, Elberg S, Finegold C (1980). Permeabilizing and hemolytic action of large and small polyene antibiotics on human erythrocytes. Antimicrob. Agents Chemother. 18:586-592.

Brajtburg J, Powderly WG, Kobayashi GS, Medoff G (1990). Amphotericin B: current understanding of mechanisms of action. Antimicrob. Agents Chemother. 34:183-8.

Burgess BL, Cavigiolio G, Fannucchi MV, Illek B, Forte TM, Oda MN (2010). A phospholipid–apolipoprotein AI nanoparticle containing amphotericin B as a drug delivery platform with cell membrane protective properties. Int. J. Pharmaceut. 399:148-155.

Burgess DS, Hastings RW, Summers KK, Hardin TC, Rinaldi MG (2000). Pharmacodynamics of fluconazole, itraconazole, and amphotericin B against Candida albicans☆. Diagnostic Microbiol. Infect. Dis. 36:13-18.

Cesaro S, Calore E, Messina C, Zanesco L (1999). Allergic reaction to the liposomal component of liposomal amphotericin B. Supportive Care in Cancer 7:284-286.

Chattopadhyay A, Jafurulla M (2011). A novel mechanism for an old drug: amphotericin B in the treatment of visceral leishmaniasis Biochem Biophys Res. Commun. 416:7-12.

Colombo AL, Nucci M, Salomão R, Branchini MLM, Richtmann R, Derossi A, Wey SB (1999). High rate of non-albicans candidemia in Brazilian tertiary care hospitals. Diagnostic Microbiol. Infect. Dis. 34:281-286

Cybulska B, Mazerski J, Borowski E, Gary-Bobo C (1984). Haemolytic activity of aromatic heptaenes: a group of polyene macrolide antifungal antibiotics. Biochem. Pharmacol. 33:41-46.

Dalazen D, Zanrosso D, Wanderley L, Silva NLD, Fuentefria AM (2011). Comparação do perfil de suscetibilidade entre isolados clínicos de Candida spp. orais e vulvovaginais no Sul do Brasil. J Bras Patol Med Lab [Internet]. J. Bras. Pat. Med. Lab. 47:33-38.

Darole PS, Hegde DD, Nair HA (2008). Formulation and evaluation of microemulsion based delivery system for amphotericin B. Aaps Pharmscitech 9:122-128.

Demaimay R, Adjou KT, Beringue V, Demart S, Lasmezas CI, Deslys J, Seman M and Dormont D (1997). Late treatment with polyene antibiotics can prolong the survival time of scrapie-infected animals. J. Virol. 71:9685-9.

Ellis D (2002). Amphotericin B: spectrum and resistance. J. Antimicrob. Chemother. 49 Suppl 1: 7-10.

Filippin FB, Souza LC (2006). Eficiência terapêutica das formulações lipídicas de anfotericina B. Rev. Bras. de Ciênc. Farm. 42:167-94.

Finquelievich J, Landaburu MF, Pinoni V, Iovannitti CA (2011). Determination of the therapeutic activity of caspofungin compared with the amphotericin B in an animal experimental model of histoplasmosis in hamster (Mesocrisetus auratus). Rev. Iberoam Micol. 28:155-158.

Fisher MA, Talbot GH, Maislin G, McKeon BP, Tynan KP, Strom BL (1989). Risk factors for amphotericin B-associated nephrotoxicity. Am. J. Med. 87:547-552.

Gray KC, Palacios DS, Dailey I, Endo MM, Uno BE, Wilcock BC, Burke MD (2012). Amphotericin primarily kills yeast by simply binding ergosterol. Proc. Natl. Acad. Sci. 109:2234-2239.
Groll AH, Giri N, Petraitis V, Petraitiene R, Candelario M, Bacher JS, Piscitelli SC, Walsh TJ (2000). Comparative efficacy and distribution of lipid formulations of amphotericin B in experimental Candida albicans infection of the central nervous system. J. Infect. Dis. 182:274-282.
Hamill RJ (2013) Amphotericin B formulations: a comparative review of efficacy and toxicity. Drugs 73:919-934.
Harbarth S, Pestotnik SL, Lloyd JF, Burke JP, Samore MH (2001). The epidemiology of nephrotoxicity associated with conventional amphotericin B therapy. Am. J. Med. 111:528-534.
Hillery AM (1997). Supramolecular lipidic drug delivery systems: From laboratory to clinic A review of the recently introduced commercial liposomal and lipid-based formulations of amphotericin B. Advanced drug delivery Rev. 24:345-363.
Holler B, Omar SA, Farid MD, Patterson MJ (2004). Effects of fluid and electrolyte management on amphotericin B-induced nephrotoxicity among extremely low birth weight infants. Pediatrics 113:e608-e616.
Huang W, Zhang Z, Han X, Tang J, Wang J, Dong S, Wang E (2002). Ion channel behavior of amphotericin B in sterol-free and cholesterol- or ergosterol-containing supported phosphatidylcholine bilayer model membranes investigated by electrochemistry and spectroscopy. Biophys. J. 83:3245-3255.
Iman M, Huang Z, Szoka FC and Jaafari MR (2011) Characterization of the colloidal properties, *in vitro* antifungal activity, antileishmanial activity and toxicity in mice of a distigmasterylhemisuccinoyl-glycero-phosphocholine liposome-intercalated amphotericin B. Int. J. pharmaceutics 408:163-172.
Inselmann G, Inselmann U, Heidemann H (2002) Amphotericin B and liver function. Eur. J. Internal Med. 13:288-292.
Janknegt R, de Marie S, Bakker-Woudenberg IA, Crommelin DJ (1992) Liposomal and lipid formulations of amphotericin B. Clin. pharmacokinetics 23:279-291.
Jung SH, Lim DH, Jung SH, Lee JE, Jeong K-S, Seong H, Shin BC (2009) Amphotericin B-entrapping lipid nanoparticles and their in vitro and in vivo characteristics. Euro. J. Pharmaceut. Sci. 37:313-320.
Kleinberg M (2006) What is the current and future status of conventional amphotericin B? Int. J. antimicrobial agents 27:12-16.
Klepser M (2011) The value of amphotericin B in the treatment of invasive fungal infections. J. critical care 26:225:e1-225. e10.
Krogh-Madsen M, Arendrup MC, Heslet L, Knudsen JD (2006a) Amphotericin B and caspofungin resistance in Candida glabrata isolates recovered from a critically ill patient. Clin. Infect. Dis. 42:938-944.
Krogh-Madsen R, Plomgaard P, Møller K, Mittendorfer B, Pedersen BK (2006b) Influence of TNF-α and IL-6 infusions on insulin sensitivity and expression of IL-18 in humans. Am. J. Physiology-Endocrinol. Metabolism 291:E108-E114.
Laing R, Milne L, Leen C, Malcolm G, Steers A (1994) Anaphylactic reactions to liposomal amphotericin. Lancet 344:682.
Lamy-Freund MT, Schreier S, Peitzsch RM, Reed WF (1991). Characterization and time dependence of amphotericin B: deoxycholate aggregation by quasielastic light scattering. J. Pharm. Sci. 80:262-266.
Laniado-Laborín R, Cabrales-Vargas MN (2009). Amphotericin B: side effects and toxicity. Revista iberoamericana de micología 26:223-227.
Legrand P, Romero EA, Cohen BE, Bolard J (1992). Effects of aggregation and solvent on the toxicity of amphotericin B to human erythrocytes. Antimicrob. Agents Chemother. 36:2518-2522.
Lemke A, Kiderlen A and Kayser O (2005). Amphotericin B. Appl. Microbiol. Biotechnol. 68:151-162.
Leon CG, Lee J, Bartlett K, Gershkovich P, Wasan EK, Zhao J, Clement JG, Wasan KM (2011). *In vitro* cytotoxicity of two novel oral formulations of Amphotericin B (iCo-009 and iCo-010) against Candida albicans, human monocytic and kidney cell lines. Lipids Health Dis. 10:1.
Lewis RE, Wiederhold NP (2003). The solubility ceiling: a rationale for continuous infusion amphotericin B therapy? Clin. Infect. Dis. 37:871-872.
Lewis RE, Wiederhold NP, Klepser ME (2005). *In vitro* pharmacodynamics of amphotericin B, itraconazole, and voriconazole against Aspergillus, Fusarium, and Scedosporium spp. Antimicrob. Agents Chemother. 49:945-951.
Longuet P, Joly V, Amirault P, Seta N, Carbon C, Yeni P (1991). Limited protection by small unilamellar liposomes against the renal tubular toxicity induced by repeated amphotericin B infusions in rats. Antimicrob. Agents Chemother. 35:1303-1308.
Louie A, Baltch A, Franke M, Smith R, Gordon M (1994) Comparative capacity of four antifungal agents to stimulate murine macrophages to produce tumour necrosis factor alpha: an effect that is attenuated by pentoxifylline, liposomal vesicles, and dexamethasone. J. Antimicrob. Chemother. 34:975-987.
Manandhar KD, Yadav TP, Prajapati VK, Kumar S, Rai M, Dube A, Srivastava ON, Sundar S (2008). Antileishmanial activity of nano-amphotericin B deoxycholate. J. Antimicrob. Chemother. 62:376-380.
Marzzullo L, Souza LC, Campa A (1997). Effect of amphotericin B associated with a lipid emulsion on the oxidative burst of human polymorphonuclear leukocytes. General Pharmacology: The Vascular System 28:203-207.
Mayer J, Doubek M, Doubek J, Horký D, Scheer P, Štěpánek M (2002). Reduced nephrotoxicity of conventional amphotericin B therapy after minimal nephroprotective measures: animal experiments and clinical study. J. Infect. Dis. 186:379-388.
Miceli MH, Chandrasekar P (2012). Safety and efficacy of liposomal amphotericin B for the empirical therapy of invasive fungal infections in immunocompromised patients. Infect. Drug Resist. 5:9-16.
Mora-Duarte J, Betts R, Rotstein C, Colombo AL, Thompson-Moya L, Smietana J, Lupinacci R, Sable C, Kartsonis N, Perfect J (2002). Comparison of caspofungin and amphotericin B for invasive candidiasis. New England J. Med. 347:2020-2029.
Moribe K, Maruyama S, Inoue Y, Suzuki T, Fukami T, Tomono K, Higashi K, Tozuka Y, Yamamoto K (2010). Ascorbyl dipalmitate/PEG-lipid nanoparticles as a novel carrier for hydrophobic drugs. Int. J. Pharmaceutics 387:236-243.
Motoyoshi M, Inaba M, Ono A, Ueno S, Shimizu N (2009). The effect of cortical bone thickness on the stability of orthodontic mini-implants and on the stress distribution in surrounding bone. Int. J. Oral Maxillofac Surg. 38:13-8.
Mukherjee AK, Gupta G, Bhattacharjee S, Guha SK, Majumder S, Adhikari A, Bhattachrya P, Majumdar SB and Majumdar S (2010). Amphotericin B regulates the host immune response in visceral leishmaniasis: reciprocal regulation of protein kinase C isoforms. J. Infect. 61:173-184.
Nahar M, Mishra D, Dubey V, Jain NK (2008) Development, characterization, and toxicity evaluation of amphotericin B–loaded gelatin nanoparticles. Nanomedicine: Nanotechnology, Biol. Med. 4:252-261.
Negri MF, Faria MG, Guilhermetti E, alves AA, paula CR, Svidzinski TIE (2010) Hemolytic activity and production of germ tubes related to pathogenic potential of clinical isolates of Candida albicans. Revista de Ciências Farmacêuticas Básica e Aplicada 31:89-93.
Odabasi Z, Karaalp A, Cermik H, Mohr J, Tigen E, Koc M, Korten V (2009) Reduction of amphotericin B-induced renal tubular apoptosis by N-acetylcysteine. Antimicrob. Agents Chemother. 53:3100-3102.
Okamoto Y, Aoki S, Mataga I (2004). Enhancement of amphotericin B activity against Candida albicans by superoxide radical. Mycopathologia 158: 9-15.
Patel GP, Crank CW, Leikin JB (2011) An evaluation of hepatotoxicity and nephrotoxicity of liposomal amphotericin B (L-AMB). J. Med. Toxicol. 7:12-15.
Patel R (1998). Antifungal agents. Part I. Amphotericin B preparations and flucytosine. Mayo Clinic Proceedings, Elsevier, pp. 1205-1225.
Sheikh S, Ali SM, Ahmad MU, Ahmad A, Mushtaq M, Paithankar M, Mandal J, Saptarishi D, Sehgal A, Maheshwari K (2010). Nanosomal Amphotericin B is an efficacious alternative to Ambisome® for fungal therapy. Int. J. Pharmaceut. 397:103-108.
Shigemi A, Matsumoto K, Ikawa K, Yaji K, Shimodozono Y, Morikawa N, Takeda Y, Yamada K (2011). Safety analysis of liposomal amphotericin B in adult patients: anaemia, thrombocytopenia, nephrotoxicity, hepatotoxicity and hypokalaemia. Int. J. Antimicrob. Agents 38:417-420.

Silveira WLL, Damasceno BPGdL, Silva KGH, Oliveira AG, Egito E (2013). Aspectos fundamentais no desenvolvimento de sistemas microemulsionados contendo anfotericina B para uso oftálmico. Revista de Ciências Farmacêuticas Básica e Aplicada 34:09-15.

Sivak O, Gershkovich P, Lin M, Wasan EK, Zhao J, Owen D, Clement JG, Wasan KM (2011). Tropically stable novel oral lipid formulation of amphotericin B (iCo-010): biodistribution and toxicity in a mouse model. Lipids Health Dis. 10:135.

Soler L, Caffrey P, McMahon HE (2008). Effects of new amphotericin analogues on the scrapie isoform of the prion protein. Biochim. Biophys. Acta. 1780:1162-1167.

Souza LC, Campa A (1999) Pharmacological parameters of intravenously administered amphotericin B in rats: comparison of the conventional formulation with amphotericin B associated with a triglyceride-rich emulsion. J. Antimicrob. Chemother. 44:77-84.

Sterling TR, Merz WG (1998) Resistance to amphotericin B: emerging clinical and microbiological patterns. Drug Resistance Updates 1:161-165.

Sundar S, Chakravarty J, Agarwal D, Rai M, Murray HW (2010) Single-dose liposomal amphotericin B for visceral leishmaniasis in India. New England J. Med. 362:504-512.

Vartivarian SE, Anaissie EJ, Bodey GP (1993). Emerging fungal pathogens in immunocompromised patients: classification, diagnosis, and management. Clin. Infect. Dis. 17Suppl 2: S487-91.

Walsh TJ, Goodman JL, Pappas P, Bekersky I, Buell DN, Roden M, Barrett J, Anaissie EJ (2001) Safety, Tolerance, and Pharmacokinetics of High-Dose Liposomal Amphotericin B (AmBisome) in Patients Infected withAspergillus Species and Other Filamentous Fungi: Maximum Tolerated Dose Study. Antimicrobial agents and chemother. 45:3487-3496.

Walsh TJ, Hiemenz JW, Seibel NL, Perfect JR, Horwith G, Lee L, Silber JL, DiNubile MJ, Reboli A, Bow E (1998) Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. Clin. Infect. Dis. 26:1383-1396.

Walsh TJ, Seibel NL, Arndt C, Harris RE, Dinubile MJ, Reboli A, Hiemenz J, Chanock SJ (1999) Amphotericin B lipid complex in pediatric patients with invasive fungal infections. The Pediatric Infect. Dis. J. 18:702-708.

Warn PA, Sharp A, Guinea J, Denning DW (2004). Effect of hypoxic conditions on in vitro susceptibility testing of amphotericin B, itraconazole and micafungin against Aspergillus and Candida. J. Antimicrob. Chemother. 53:743-749.

Wasan K, Vadiei K, Lopez-Berestein G, Verani R, Luke D (1990) Pentoxifylline in amphotericin B toxicity rat model. Antimicrob. Agents Chemother. 34:241-244.

Wayne P (2002) National committee for clinical laboratory standards. Performance standards for antimicrobial disc susceptibility testing 12.

White MH, Bowden RA, Sandler ES, Graham ML, Noskin GA, Wingard JR, Goldman M, van Burik J-A, McCabe A, Lin J-S (1998). Randomized, double-blind clinical trial of amphotericin B colloidal dispersion vs. amphotericin B in the empirical treatment of fever and neutropenia. Clin. Infect. Dis. 27:296-302.

White TC, Marr KA, Bowden RA (1998). Clinical, cellular, and molecular factors that contribute to antifungal drug resistance. Clin. Microbiol. Rev. 11:382-402.

Wiederhold NP, Tam VH, Chi J, Prince RA, Kontoyiannis DP, Lewis RE (2006). Pharmacodynamic activity of amphotericin B deoxycholate is associated with peak plasma concentrations in a neutropenic murine model of invasive pulmonary aspergillosis. Antimicrob. Agents Chemother. 50:469-473.

Xu N, Gu J, Zhu Y, Wen H, Ren Q, Chen J (2011). Efficacy of intravenous amphotericin B-polybutylcyanoacrylate nanoparticles against cryptococcal meningitis in mice. Int. J. Nanomed. 6:905-913.

Yano T, Itoh Y, Kawamura E, Maeda A, Egashira N, Nishida M, Kurose H and Oishi R (2009). Amphotericin B-induced renal tubular cell injury is mediated by Na+ Influx through ion-permeable pores and subsequent activation of mitogen-activated protein kinases and elevation of intracellular Ca2+ concentration. Antimicrob Agents Chemother. 53:1420-1426.

African Journal of Pharmacy and Pharmacology

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*
- *Journal of Pharmacognosy and Phytotherapy*
- *Journal of Toxicology and Environmental Health Sciences*

academicJournals