ASSESSMENT OF TOXICITIES ASSOCIATED WITH AMPHOTERICIN B ADMINISTRATION AMONG HIV INFECTED ADULTS WITH CRYPTOCOCCAL MENINGITIS AT KIAMBU DISTRICT HOSPITAL

BY
AGNES WAMBUI, B.PHARM
U56/69005/2013

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Award of the Degree of Master of Pharmacy in Clinical Pharmacy in the School of Pharmacy, University of Nairobi.

November 2015
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U56/69005/2013

Signature................................... Date....................................

APPROVAL BY SUPERVISORS

1. Dr. David G. Nyamu, MPharm

   Department of Pharmaceutics and Pharmacy Practice
   University of Nairobi

   Signature................................... Date....................................

2. DR. Peter N. Karimi, MPharm, Msc, MBA

   Department of Pharmaceutics and Pharmacy Practice
   University of Nairobi

   Signature................................... Date....................................


DEDICATION

I dedicate this work to my family; my husband George Karita, my sons Michael, Daniel, my parents, brothers and sisters for your love, prayers and encouragement.
ACKNOWLEDGEMENT

I acknowledge the Almighty God for giving me the strength, attitude and zeal to pursue this course.
I wish to sincerely thank my supervisors Dr. Nyamu and Dr. Karimi for their guidance, mentorship, invaluable time, support and advice towards the preparation of this dissertation. I wish to thank the staff of Kiambu district hospital for their help towards data collection.
ABBREVIATIONS AND ACRONYMS

AIDS- Acquired Immunodeficiency Syndrome
BUN- Blood Urea Nitrogen
CCC- Comprehensive Care Centre
CDC- Centre for Diseases Control
Cryptococcal Meningitis- Cryptococcal Meningitis
CSF- Cerebral Spinal Fluid
GFR- Glomerular Filtration Rate
HIV- Human Immunodeficiency Virus
IV- Intravenous
KCl- Potassium chloride
KDH- Kiambu District Hospital
Kg- Kilogram
KNH- Kenyatta National Hospital
NASCOP- National AIDS & STI Control Programme
NSAIDS- Non Steroidal Anti-inflammatory Drugs
TB- Tuberculosis
USAID- United State Agency for International development
UON- University of Nairobi
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ABSTRACT

**Background:** HIV infection is a worldwide epidemic with the highest prevalence in sub-Saharan Africa. This has in turn increased prevalence of Cryptococcal meningitis which is a common AIDS related opportunistic infections with a high morbidity and mortality rate. Amphotericin B is the gold standard in the management of Cryptococcal meningitis but its use is limited by toxicities resulting from a number of factors such as cumulative dosage and concomitant drugs. Several strategies, including premedication and monitoring of electrolytes, have been proposed for preventing these toxicities. Published local studies on assessment of toxicities remain scanty.

**Objectives:** The main objective of the study was to assess toxicities associated with amphotericin B in the management of Cryptococcal meningitis among HIV infected adults aged 18 years and over in Kiambu District Hospital.

**Methodology**

A cross sectional retrospective design was used that involved review of patients’ records at Kiambu District Hospital medical records department. All the one hundred and six files of adult HIV infected patients with Cryptococcal meningitis and treated with amphotericin B were used. Data on amphotericin B toxicities, risk factors and preventive strategies for toxicities were extracted from the files using a predesigned semi-structured data collection form. This data was entered into Microsoft Access version 2013 to create a database and then exported to Statistical Package for Social Sciences Version 22.0 for analysis. Statistical significance was determined at 95% confidence level and values with P≤0.05 were regarded as statistically significant.

**Results**

The female to male ratio was approximately equal females being 54(50.9%). Prevalence of infusion related toxicities was high at 87.7%, with fever being the most common at 58.1%. Prevalence of nephrotoxicity was at 27.4%, with hypokalemia at 41.4% and increased creatinine at 58.6%. Amphotericin B dose was an important risk factor for toxicity (p=0.045). Potassium monitoring (p=0.028), creatinine monitoring (p=0.019) and fluid monitoring (p=0.026) were observed to be important factors in preventing the toxicity. Baseline monitoring was over 70% of the cases but monitoring during course of treatment was below 20%.

**Conclusion and recommendation**
Prevalence of toxicity of amphotericin B in Kiambu District Hospital is high. Since amphotericin B dosage is an important predictor of toxicity clinicians should be encouraged to be more cautious when dosing amphotericin B and in particular, use the patient weight based dosing as per treatment guidelines. In addition, patient monitoring, hydration and premedication are key in preventing the toxicity and should be encouraged.
CHAPTER 1: INTRODUCTION

1.1: Background

amphotericin B is a natural antibiotic belonging to polyene macrolide group. It was isolated in 1955 from Actinomycete *Streptomyces nodosus* and acts primarily by binding to ergosterol (1,2). It is used in the management of severe and life-threatening systemic fungal infection because of its broad fungicidal activity and cost effectiveness (3).

This drug is poorly absorbed in the gastrointestinal tract and the volume of distribution is approximately 4L per Kg body weight (4). Plasma half-life is 24 hours, and on long term use the terminal half-life is 15 days. Unchanged amphotericin B is excreted in small amounts in the urine. It is not removed by haemodialysis (5). The pure form of the drug has very little solubility in aqueous form at physiologic PH requiring complexing with other agents for clinical use (6,7). amphotericin B is the treatment of choice in management of Cryptococcal Meningitis (8–10). According to The Infectious Diseases Society for America’s the dosage in the treatment of Cryptococcal meningitis should be 0.7 mg/kg per day of amphotericin B deoxycholate (11,12). The toxicities can either be infusion related or due to kidney damage. Infusion related toxicities include fever, headache, nausea, chills, malaise, hypertension, hypotension, cardiac arrhythmias, and skin rashes (13). Nephrotoxicity involves tubular and glomerular damage. They can be reversible or irreversible particularly in patients given large cumulative doses above 5g (14). Renal manifestation include hypokalemia, hypomagnesaemia, renal tubular acidosis and uric acid excretion which can cause nephrocalcinosis (15,16) Reversible normocytic normochromic anemia develops in most patients due to direct suppressive effect on erythropoietin production (17).

There has been a significant increase in cases of Cryptococcal meningitis which is among the common opportunistic infection in HIV especially in Africa and South East Asia due to poor resource settings (18). Mortality from Cryptococcal meningitis is high. The Center for Disease Control (CDC) cites that out of an estimated worldwide one million cases of Cryptococcal meningitis per year among people with HIV/AIDS, nearly 625,000 results in death. However, the highest mortality rate is in Sub–Saharan Africa, where mortality is projected to be between 50% and 70% (19). A prospective observational study done in Kenya to determine the clinical features, risk factors and outcomes of Cryptococcal meningitis found out that incidence of Cryptococcal
meningitis was 33% and mortality was 36%. The study concluded that there was high incidence of Cryptococcal Meningitis in Kenyatta National Hospital (KNH) and Mbagathi District Hospital (20).

1.2: Problem statement
The high prevalence of HIV has increased the prevalence of Cryptococcal Meningitis. Amphotericin-B is a critical agent in the management of Cryptococcal Meningitis. Ideally amphotericin-B should cure Cryptococcal Meningitis with minimal harm. However, studies have shown that amphotericin B increases and prevalence of toxicities is high (21). Toxicities causes increased morbidity, mortality, length of hospital stay and cost of seeking treatment (22). From hospital records in KDH there are 2504 patients with HIV, these increases Cryptococcal Meningitis cases and amphotericin-B toxicity. Awareness of treatment guidelines and having standard operating procedures by health care workers can reduce the toxicities of amphotericin B. HIV/AIDS patients are prone to drug toxicity due to the high pill burden and drug interactions. It is probable that this group of patients experience a high risk of amphotericin B induced toxicity.

1.3: Justification for the study
The use of amphotericin B is limited by toxicity, for instance, elevated creatinine which is not only a marker of renal dysfunction but also linked to an increase in hospital costs and substantial risk for hemodialysis and a higher mortality rate hence, prevention is essential (22). The study will help in improving management of Cryptococcal Meningitis in HIV infected patients who are more prone to drug toxicities, by identifying the risk factors for toxicity and preventive strategies that can be used against these toxicities. The study will also seek to quantify the magnitude of the problem in KDH which will help in understanding the burden of the toxicity in the county. Recent studies have shown liposomal formulations, despite being less available and more expensive, are more tolerable than deoxycholate formulation. The latter is more commonly used and is associated with a number of toxicities. There are limited published literature on the safety studies of amphotericin B in Kenya.

1.4: Objectives
1.4.1: Broad objective
To assess toxicities associated with amphotericin B administration among HIV infected adults with Cryptococcal meningitis at Kiambu District Hospital.
1.4.2: Specific objectives

1. To determine the prevalence of amphotericin B toxicity in KDH.
2. To identify the risk factors associated with amphotericin B toxicity in KDH.
3. To describe the preventive strategies against amphotericin B toxicity in KDH.

1.5: Research questions

1. What is the prevalence of amphotericin B toxicity in KDH?

2. What are the risk factors associated with amphotericin B toxicity in KDH?

3. What are the preventive strategies used in KDH in preventing amphotericin B toxicity?
CHAPTER 2: LITERATURE REVIEW

2.1: Introduction
This chapter comprises of various findings on the amphotericin B toxicity both infusion and nephrotoxicity profiles. It also outlines the various studies on risk factors for toxicity and the various preventive strategies to minimize the toxicity.

2.2: Amphotericin B toxicity
The use of amphotericin B is limited by infusion-related toxicities (13) Infusion related toxicities are observed during the infusion of the drug or shortly after the infusion. These toxicities can be attributed to pro-inflammatory cytokine production. A double blind placebo controlled clinical trial demonstrated that ibuprofen which is a potent inhibitor of prostaglandin synthesis administered 30 minutes before amphotericin B administration reduced incidence of fever and chills. The study concluded that chills and fever are mediated by prostaglandin E2 and ibuprofen is therapeutically useful in ameliorating these toxicities but this is not a promising avenue in humans due to NSAIDS induced nephrotoxicity (23). The selective inhibition of thromboxane’s formation would appear a more promising avenue for future study(24).

Infusion-related reactions cause increased hospitalization and mortality leading to increase in treatment costs (25). To reduce these effects several strategies have been adopted. A study done by Pathak et al., 1998, found out that only 23% of patients needed premedication. New and expensive formulation should be reserved for the small subset of patients who either are intolerant to amphotericin B deoxycholate or need high doses for systemic infection (26). In another study done to determine the premedication practices and incidence of infusion-related reactions in patients receiving amphotericin B concluded that corticosteroid reduce infusion-related reactions given as a premedication while paracetamol and antihistamines, although commonly used are not useful (27).

The prevalence for infusion-related toxicities has been quoted as 71% in several studies (6,28). A prospective study of patients on amphotericin B found out that 71% developed at least one infusion related reaction. The most common reactions were fever, chills, nausea, headache and thrombophlebitis (29) also in another study by Mayer 1999, the frequency of infusion-related, toxicity was minimal relative to other reports A study done at Kenyatta National Hospital (KNH) to
determine the toxicity and efficacy of amphotericin B in HIV positive patients found a prevalence of 70.1% (21).

Incidence and severity of amphotericin B nephrotoxicity is high. A study conducted at KNH found the incidence of renal dysfunction, hypokalemia, hypomagnesaemia in acquired immunodeficiency syndrome patients with Cryptococcal meningitis was common (30). Among the participants, 58.6% had at least 100% increase in serum creatinine, 38.6% had 50%, 93% had hypokalemia and 80% developed hypomagnesaemia. Only 54.3% completed the 14 day treatment.

Amphotericin B nephrotoxicity manifests as reduction in glomerular filtration rate and tubular dysfunction (31). GFR reduction is due to renal vasoconstriction during drug infusion. Tubular dysfunction is due to direct interaction of amphotericin B with the cholesterol on the tubular cell membrane. (24). The interaction between these two mechanisms occurs via tubule glomerular feedback in which low sodium delivery to macula densa cells caused by proximal tubular dysfunction enhances afferent vasoconstriction thereby decreasing renal blood flow (16,32). Indirect secondary effects that activate intrarenal mechanism and cause an increase in mediators are also thought to play part. The mediators like thromboxane A2 results in reduced blood flow and filtration rate (16).

Nephrotoxicity causes several renal failure problems especially acute renal failure (33–36). In a study by Wingard et al., more than 50% of patients had an increase in serum creatinine as compared to baseline, a decrease in renal function of 70% and more than 155 of the patients required dialysis in the study and the need for dialysis also increased mortality by three fold (33).

The mortality and costs of treating acute renal failure are high (22). Death occurs frequently in patients who develop the condition while receiving the drug. Additional length of stay and costs associated with therapy are high. This data make clear the costs of this complication and suggest that alternative agents that reduce its frequency may be cost-effective, especially among patients at high risk of developing renal failure (37).

A retrospective cohort observational study comparing adverse events and hospital length of stay associated with the various amphotericin B formulations found out that patients on Conventional amphotericin B had longer length of stay than lipid formulation. The risk factors for nephrotoxicity were patients average daily amphotericin dose, dehydration, cumulative dose, abnormal baseline
renal function, concomitant nephrotoxic drugs and male gender (38). The incidence of nephrotoxicity rises with an increase in the number of risk factors suggesting that an alternative therapy might be appropriate in patients with two or more risk factors (39).

The different formulations of amphotericin B are the conventional form and the lipid formulation. The three lipid formulations are Liposomal amphotericin (AmBisome), amphotericin B lipid complex and amphotericin B colloidal dispersion. A study conducted by Veerareddy et al., 1998, on lipid based formulations of amphotericin B concluded that colloidal dispersion was less nephrotoxic but the infusion related toxicities were as frequent and severe to those of amphotericin B. The complex effectiveness was similar to conventional amphotericin B but was more tolerable. AmBisome was similar or superior in efficacy to conventional amphotericin B. Renal and general tolerability was excellent. The major drawback for these formulations is cost and there is need to develop more affordable lipid formulation (40).

Another study by Moen 2009, concluded that further pharmacoeconomic studies are needed to fully define cost effectiveness (41). The optimal dosing regimen for the lipid formulations is unclear but a dose range of 3-5mg/kg/day is given (42). The three lipid formulation differ in the lipid composition and their pharmacokinetics differ substantially (43). A systematic review to examine renal function in patients with invasive fungal infections comparing Conventional amphotericin B and the lipid formulation concluded that lipid formulation of amphotericin B are an important strategy of preserving renal function and improving survival in critically ill patient (44).

2.3: Risk factors for toxicity

There are several factors that predispose to amphotericin B nephrotoxicity. A case control study by Fisher et al., 1989, concluded that higher average daily dose, diuretic use, abnormal renal function are among the risk factors for toxicity (38). In another study for determining risk factor for amphotericin B toxicity in patients who received intravenous amphotericin B for more than three days and a total cumulative dosage greater than 100mg concluded that nephrotoxicity was associated with a greater cumulative dose of amphotericin B and concomitant use of nephrotoxic drugs. Among patients with severe nephrotoxicity, cyclosporine was the greatest risk factor (45).
2.4: Prevention and management of toxicities

Preventive strategies have been documented for preventing both infusion related nephrotoxicity. A study by Costa 2001, found out that sodium supplementation, low dose dopamine, slower infusion rates administration of amphotericin B in lipid emulsion and lipid formulation reduce nephrotoxicity (46). Several studies including meta-analysis and systematic review have shown that the use of a liposomal formulation has fewer side effects compared to deoxycholate formulation (43,47–49). The meta-analysis showed that the lipid-based formulation reduced the causal mortality by an estimated 28% compared to Conventional amphotericin B (49). Although several studies have demonstrated that the lipid formulation are more tolerable, another study concluded that toxicity of Conventional amphotericin B is tolerable, cost less and can be used safely provided there is suitable premedication and monitoring of blood urea nitrogen, serum potassium and magnesium levels (50).

There are several studies demonstrating the protective effect of sodium loading on reducing nephrotoxicity (51). A study on salt loading and infusion period effectiveness in preventing nephrotoxicity concluded that salt loading prevents glomerular toxicity and has no effect on tubular toxicity (52). A study conducted by Berdichevski et al., 2006, found that in low risk patients who are hemodynamically stable with normal renal function and not in intensive care unit, use of expensive therapies was not justified. Concurrent use of amphotericin B with prophylactic sodium chloride loading was associated with small reversible decrease in renal function (53).

Continuous infusion rate has been shown to reduce infusion related toxicities (13,54,55). In a study to compare effects of amphotericin B deoxycholate infused over 4 hours concluded that continuous infusion is better tolerated than rapid infusion although the results were based on a small sample size and the study was not blinded for practical reasons. These could have lowered the quality of the study and its validity (56). Another study done by Craven et al., 1985, concluded that infusion rates do not modify amphotericin B toxicity but in patients with acute renal failure rapid infusion cause severe hyperkalemia and fatal arrhythmias (57).

There is controversy on whether premedication practices should be used before amphotericin B administration. One study concluded that empirical premedication for infusion related toxicities associated with amphotericin B cannot be routinely advocated. Instead patient should be treated when symptoms first arise and then premedicated for subsequent amphotericin B infusions (29). In another study by Grasela et al., 1990, premedication were used to prevent infusion related events and
concluded that pretreatment may minimize these adverse events and prevent a complete evaluation of a test dose (6). A prospective study on the drug delivery reaction concluded that premedication with hydrocortisone results in low incidence of drug delivery reaction (58).

According to 2013 update guidelines for the prevention, diagnosis and management of Cryptococcal meningitis among HIV infected persons there are several strategies for preventing toxicities (59) The guidelines recommended that patients should be prehydrated with one liter of normal saline containing one ampoule of Potassium chloride infused two hours before amphotericin B deoxycholate, to reduce renal toxicity and hypokalemia. The guidelines also recommend clinical and laboratory monitoring of baseline serum creatinine, potassium and haemoglobin. On the minimum, twice weekly monitoring of potassium, serum creatinine and weekly haemoglobin should be carried out. Fluid input and output chart should be used for monitoring (59).
CHAPTER THREE: METHODOLOGY

3.1: Introduction
This chapter describes the research design, target population, eligibility criteria and sampling of study subjects, as well as the methods of data collection, analysis and presentation that were used in this study.

3.2: Study design
A retrospective cross sectional design involving review of records was used. Patient files from January 2010 to December 2014 were assessed and data on demographics, risk factors and preventive strategies entered in the data collection form.

3.3: Study site
The study was conducted in Kiambu District Hospital. It is a level 4 district hospital located in Kiambu Town, Kiambu County. It is managed by County Government of Kiambu. It has capacity of 298 beds with two medical wards, two surgical wards, maternity, paediatric and gynecological ward. There are 42 daily admissions and 196 outpatients. The hospital has a comprehensive care centre (CCC) with a total of 2504 patients, which includes 2194 adults and 310 children from the hospital records. From anecdotal evidence use of amphotericin B and mortality from Cryptococcal meningitis is high.

3.4: Study population
The target population was adult HIV positive patients, with Cryptococcal meningitis who were treated with amphotericin B while admitted in Kiambu District Hospital between January 2010 and December 2014.

3.5: Inclusion criteria
1. Patients aged 18 years and above.
2. HIV positive patients with a diagnosis of Cryptococcal meningitis.

3.6: Exclusion criteria
1. Evidence of renal failure
2. Patient aged less than 18 years

3.7: Sample size estimation

According to a local study done by Anish et al.,(21), the prevalence of amphotericin B toxicity was 70%. Karl Fischer’s formula was used for estimating the sample size.

\[ n_0 = \frac{Z^2 P (1-P)}{d^2} \]

Where:
- \( n \) is the total sample required for the study
- \( n_0 \) sample size before adjusting for finite population
- \( Z \) is the standard normal deviation corresponding to 95 % confidence level (\( Z = 1.96 \)).
- \( P \) is the prevalence of amphotericin B toxicity.
- \( d \) is the difference that needs to be observed.

\[ Z = 1.96, \ P = 0.7, \ 1-P = 0.3, \ d = 0.05 \]

Thus;

\[ n_0 = \frac{1.96 \times 1.96 \times 0.7 \times 0.3}{0.05 \times 0.05} \]

\[ n_0 = 322.7 \]

\[ n_0 = 323 \]

Adjusting for finite population

\[ n = \frac{n_0 \times N}{n_0 + (N-1)} \]

Where \( N \) is population size

\[ n = \frac{323 \times 106}{(323 + 105)} = 80 \]

With 80 people it would have been possible to make generalisable conclusions at KDH. To enhance the generalizability of the results, a sample size of 106 files was used.

3.8: Sampling technique

A list of all Cryptococcal meningitis cases starting from December 2014 and going back until January 2010 was generated from the medical records department. These file numbers were presented to the medical records for retrieval. The files were assessed for eligibility criteria and the files that met the study inclusion criteria were selected using simple random sampling technique. A total of 106 files were selected for data collection.
3.9: Data collection and management

Data was collected using a semi-structured form (appendix 2). Data on demographics, risk factors and preventive strategies was picked. Data collection forms did not have patient identifiers but a unique code. Filled data collection sheets were stored in a lockable cabinet. Data was entered into a password protected Microsoft Access 2013 database. To ensure accuracy, once entry was completed, the Principal Investigator compared the entered data with the hard copy forms. The hard copy data collection forms were kept in a locked file cabinet and keys kept in a different secure location. To ensure safety of the electronic data the password was changed regularly and administration rights were restricted. The system was protected by keeping updated antivirus, updated software and the data was backed up every day in a hard disk which was kept in a different location.

3.10: Data analysis

The study population was described by performing exploratory data analysis. Continuous variables such as age, weight are described using measures of central tendency and dispersion (Mean, Median, Minimum, Maximum, and Inter Quartile Range). Categorical variables such as gender, marital status are summarized using frequencies and percentages. The results are presented in tables and charts. To determine the prevalence of amphotericin B toxicity in HIV positive patients who had Cryptococcal meningitis, the proportion of patients with infusion related toxicities and nephrotoxicity was calculated. To identify risk factors for amphotericin B toxicity bivariate analysis was conducted using all dependent variables before multivariate analysis to determine independent predictors. During bivariate analysis, Chi-squared test was used to determine association of amphotericin B toxicity with categorical variables while analysis of variance (ANOVA) test was used to determine association with continuous variables. Multivariate analysis was conducted using backward stepwise binary logistic regression with amphotericin B toxicity as the outcome variable and the factors that were significant as predictors.

3.11: Quality assurance

All aspects of quality assurance were adhered to. A pilot study was conducted to determine reliability of data collection tool and any error noted was modified in the data collection form. Appropriate documentation was maintained at all times. External validity was ensured through appropriate non-biased sampling and adequate sample size. Patient files from where data was extracted were kept safely under lock and key and review of patient files was done within the
hospitals records department to ensure confidentiality. Patients’ names were not entered in the data collection form but coded for purposes of further maintaining confidentiality. All information obtained from the files was kept confidentially.

3.12: Ethical considerations

Approval for conducting the research was sought and granted from the Kenyatta National Hospital – University of Nairobi Ethics and Research Committee (KNH/UoN-ERC) (appendix 3) and Kiambu District Hospital (appendix 4) before commencing the study. There were no direct benefits or risks to the patients during the study. No events of clinical importance were discovered during the study. Consent forms were not applicable because only patient files were used in the study. Confidentiality of the patient files was kept by using study numbers. The data collected from the patient files was stored securely.
CHAPTER 4: RESULTS

4.1: Introduction

This chapter reports the study findings on amphotericin B toxicities and is summarized in Tables and Figures. One hundred and six files were used and both univariate and bivariate analysis used.

4.2: Baseline population characteristics

There were 54(50.9%) females as portrayed in Table 1. The mean age of the study participants was 37.4 Standard Deviation (SD) 8.9 years. The median age was 35 years Inter Quartile Range (IQR) 32-43. Majority of the population were aged between 18-35years accounting for 53(52.5%) of the study population. Majority of the participants were married and unemployed but had attained some level of education.

Table 1: Social demographic characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Category</th>
<th>Frequency(n)</th>
<th>Percentage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>49</td>
<td>46.2%</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>54</td>
<td>50.9%</td>
</tr>
<tr>
<td></td>
<td>Not indicated</td>
<td>3</td>
<td>2.8%</td>
</tr>
<tr>
<td>Marital status</td>
<td>Single</td>
<td>22</td>
<td>25.9%</td>
</tr>
<tr>
<td></td>
<td>Married</td>
<td>55</td>
<td>64.7%</td>
</tr>
<tr>
<td></td>
<td>Separated</td>
<td>3</td>
<td>3.5%</td>
</tr>
<tr>
<td></td>
<td>Divorced</td>
<td>3</td>
<td>3.5%</td>
</tr>
<tr>
<td></td>
<td>Widowed</td>
<td>2</td>
<td>2.4%</td>
</tr>
<tr>
<td>Employment</td>
<td>Employed</td>
<td>11</td>
<td>17.7%</td>
</tr>
<tr>
<td></td>
<td>Self-employed</td>
<td>16</td>
<td>25.8%</td>
</tr>
<tr>
<td></td>
<td>Unemployed</td>
<td>35</td>
<td>56.5%</td>
</tr>
<tr>
<td>Religion</td>
<td>Christian</td>
<td>70</td>
<td>100.0%</td>
</tr>
<tr>
<td></td>
<td>Muslim</td>
<td>0</td>
<td>0.0%</td>
</tr>
<tr>
<td>Education level</td>
<td>Informal</td>
<td>5</td>
<td>17.9%</td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>10</td>
<td>35.7%</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>11</td>
<td>39.3%</td>
</tr>
<tr>
<td></td>
<td>College and above</td>
<td>2</td>
<td>7.1%</td>
</tr>
<tr>
<td>Age group</td>
<td>18-35 years</td>
<td>53</td>
<td>52.5%</td>
</tr>
<tr>
<td></td>
<td>36-65 years</td>
<td>47</td>
<td>46.5%</td>
</tr>
<tr>
<td></td>
<td>&gt;65 years</td>
<td>1</td>
<td>1.0%</td>
</tr>
</tbody>
</table>
4.3: Risk factors for amphotericin B toxicity

4.3.1: Concomitant drugs used

The most common concomitant drugs (Appendix 5) were antibiotics at 84.9% (Figure 1), with cotrimoxazole being the most prevalent followed by benzylpenicillin, chloramphenicol. Antibiotics were followed by antiretrovirals.

![Prevalence of concomitant drugs](image)

**Figure 1: Prevalence of Concomitant Drugs Used by Study Participants**
4.3.2: Prevalence of comorbidities

The most common comorbidity was TB with a prevalence of 25(56.8%), followed by pneumonia at 20.5% (Figure 2). The other diseases in order were candidiasis, gastroenteritis, anaemia and herpes.

![Figure 2: Prevalence of comorbidities](image)

4.3.3: Level of CD4 cells

Out of 106 patients only 10 had their CD4 counts determined and half of these had a CD4 cells count above 100/mm$^3$ while 30% had below 50 cells/mm$^3$

4.4: Prevalence of toxicity

4.4.1: Infusion toxicities related due to amphotericin B administration

The most common infusion related toxicities was fever at 62(58.5%) followed by headache (49.1 %), nausea and hypotension (Figure 3). Others were chills, thrombophlebitis, anaemia and hypotension.
Most of the patients’ experienced more than one infusion related toxicities (Table 2). Only 13 (12.3%) did not experience infusion related toxicities. Those who experienced two infusion related toxicities were 32 (30.2%). Overall infusion related toxicities were experienced by 93 (87.7%) of the respondents.

### Table 2: Number of infusion related toxicities

<table>
<thead>
<tr>
<th>Number of infusion related toxicities</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>13</td>
<td>12.3</td>
</tr>
<tr>
<td>1</td>
<td>30</td>
<td>28.3</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>30.2</td>
</tr>
<tr>
<td>3</td>
<td>24</td>
<td>22.6</td>
</tr>
<tr>
<td>4</td>
<td>5</td>
<td>4.7</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>0.9</td>
</tr>
</tbody>
</table>

### 4.4.3: Prevalence of nephrotoxicity

Nephrotoxicity was seen in 29 (27.4%) patients, and the most common presentations were elevated serum creatinine for 17 (58.6%) and hypokalemia at 12 (41.4%).

---

**Figure 3: Infusion related toxicities**

- Fever: 58.5%
- Headache: 49.1%
- Nausea/vomiting: 25.5%
- Hypertension: 20.8%
- Chills: 6.6%
- Thrombophlebitis: 2.8%
- Anemia: 1.9%
- Hypertension: 1.9%
- Others: 18.9%

- Percentage (%)
4.5: Preventive strategies against development of nephrotoxicity

4.5.1: Monitoring of parameters

Before commencing treatment with amphotericin B, haemoglobin, creatinine, potassium and blood urea nitrogen were measured in over 70% of cases (Figure 4).

![Parameters monitored within the course of treatment](image)

**Figure 4: Frequency of monitoring of parameters during the course of 14 day treatment**

During the course of the treatment very few parameters were monitored. Haemoglobin was monitored twice in twenty (18.9%) of the patients and thrice among four (3.8%). Creatinine was monitored once in (70.0%) patients and twice in thirteen (12.3%) of the respondents during the 14 day treatment. The frequency of patients monitoring decreased over time in the course of the 14 day treatment.

Fluid input and output monitoring was done in 32(30.2%) of the cases.
4.5.2: Pre-treatment as a preventive strategy to amphotericin B toxicity
The most common pretreatments were salt loading in 87(82.1%) followed by analgesics 48(45.3%) and potassium chloride at 36(34%) as shown in (figure 5).

![Pretreatment Given During Treatment](image)

Figure 5: Pretreatments given during treatment

4.6: Outcomes of therapy with amphotericin B
Those who were cured were 62.9% and the rest died. Most of the toxicities were treated (33%). Others resolved spontaneously at 22% (Figure 6). Death due to toxicity was reported in 13% while only 1% stopped amphotericin B administration and were given only fluconazole.

![Outcome of toxicity](image)
Figure 6: Outcome of Toxicity

4.7: Bivariate analysis

4.7.1: Association between age and outcome of therapy

There was no statistically significant association between patients age and development of amphotericin B toxicity ($P=0.379$) (Table 3).

<table>
<thead>
<tr>
<th>Outcome of therapy</th>
<th>Cured</th>
<th></th>
<th>Death</th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Age group(years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-35</td>
<td>32</td>
<td>69.6</td>
<td>14</td>
<td>30.4</td>
<td>0.379</td>
</tr>
<tr>
<td>36-65</td>
<td>26</td>
<td>57.8</td>
<td>19</td>
<td>42.2</td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>1</td>
<td>100.0</td>
<td>0</td>
<td>.0</td>
<td></td>
</tr>
</tbody>
</table>

4.7.2: Factors associated with toxicity

According to this study, the only predictor for infusion related toxicity was total daily dosage of amphotericin B of 50mg ($p=0.045$). Age ($p=0.422$) and weight ($p=0.256$) were not statistically significantly associated with toxicity with (Table 4).

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Toxicity</th>
<th>n</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of the patient(Years)</td>
<td>No</td>
<td>19</td>
<td>35.9</td>
<td>8.3</td>
<td>0.422</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>82</td>
<td>37.7</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td>Weight of Patient(Kg)</td>
<td>No</td>
<td>2</td>
<td>63.0</td>
<td>9.9</td>
<td>0.256</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>4</td>
<td>49.5</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td>Total daily dose of amphotericin B 50(mg)</td>
<td>No</td>
<td>11</td>
<td>52.7</td>
<td>6.5</td>
<td>0.045</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>43</td>
<td>47.7</td>
<td>7.4</td>
<td></td>
</tr>
</tbody>
</table>
4.7.3: Factors associated with nephrotoxicity

Participants’ employment status, fluid, potassium, creatinine and BUN monitoring had statistically significant associations with the development of nephrotoxicity (p values <0.05). Gender, marital status, education level, salt loading and KCl did not have any statistically significant association with development of nephrotoxicity (Table 5).

Table 5: Bivariate analysis for factors associated with nephrotoxicity

<table>
<thead>
<tr>
<th></th>
<th>No nephrotoxicity</th>
<th>Nephrotoxicity Developed</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>Female</td>
<td>47</td>
<td>7</td>
</tr>
<tr>
<td><strong>Salt loading</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>Yes</td>
<td>70</td>
<td>17</td>
</tr>
<tr>
<td><strong>KCl</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>58</td>
<td>12</td>
</tr>
<tr>
<td>Yes</td>
<td>27</td>
<td>9</td>
</tr>
<tr>
<td><strong>Fluid input and output monitoring</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>65</td>
<td>9</td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td><strong>Creatinine Monitoring</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>63</td>
<td>10</td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
<td>11</td>
</tr>
<tr>
<td><strong>Potassium monitoring</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>65</td>
<td>11</td>
</tr>
<tr>
<td>Yes</td>
<td>20</td>
<td>10</td>
</tr>
<tr>
<td><strong>Blood urea Nitrogen measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>62</td>
<td>10</td>
</tr>
<tr>
<td>Yes</td>
<td>23</td>
<td>11</td>
</tr>
</tbody>
</table>

4.8: Multivariate analysis on the factors associated with development of nephrotoxicity

Binary logistic regression was done to identify independent factors associated with development of nephrotoxicity. Patients whose fluids were monitored were 4 times more likely to be free from nephrotoxicity {OR=4.4 [95% CI; 1.6 – 12.5], p=0.005}. Patients whose potassium levels were monitored were 3 times more likely to be free from nephrotoxicity {OR=3.0 [95% CI; 1.1 – 8.7], p=0.037} as shown in (table 6).

Table 6: Factors independently associated with nephrotoxicity

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>S.E. of coefficient</th>
<th>p-value</th>
<th>OR</th>
<th>95% CI for OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluid monitoring</td>
<td>1.492</td>
<td>.526</td>
<td>.005</td>
<td>4.448</td>
<td>1.587 – 12.464</td>
</tr>
<tr>
<td>Potassium monitoring</td>
<td>1.119</td>
<td>.535</td>
<td>.037</td>
<td>3.062</td>
<td>1.072 – 8.744</td>
</tr>
</tbody>
</table>

Key: CI (confidence interval), OR (odds ratio), SE (standard error),
CHAPTER 5: DISCUSSION, CONCLUSION AND RECOMMENDATIONS

5.1: Introduction
This chapter discusses the study results and compares them with other findings done elsewhere. It also tries to explain the disparities between study findings and results from other studies and offers scientific explanation for the study findings. Conclusions and recommendations are also included.

5.2: Discussion
The study population was distributed almost equally between both genders. The mean age was 37.4 years (SD 8.9). Most participants were married and unemployed a similar study done at KNH showed similar results (21).

The most common concomitant drugs used were antibiotics with cotrimoxazole being the most prevalent because it is used in both prophylaxis and treatment of opportunistic infections. The common opportunistic infections among the HIV infected patients are Pneumocystis jiroveci pneumonia, toxoplasmosis and many bacterial infections including TB. Tuberculosis was the most prevalent comorbidity as found elsewhere (21) being a common opportunistic infections in HIV infected patients. The use of cotrimoxazole was followed by a combination of benzyl penicillin and chloramphenicol since before Cryptococcal Meningitis confirmation the patients had been treated empirically for bacterial meningitis. A study done by Anish et al., at KNH, reported a similar finding (21).

This study reports that the infusion related toxicity prevalence was high at 87.7% and fever was the most common followed by headache. This finding compares favorably to previous studies done that reported toxicity prevalence of 71 % with the most common being fever, chills, nausea and headache (6, 13, 28). This study findings showed a nephrotoxicity prevalence of 27.4% unlike in a previous study done at KNH which showed a prevalence of 70.1% (30). The difference in the results may be due to erratic monitoring in this study such that parameters suggestive of nephrotoxicity could have been missed out. No statistically significant relationship was showed between patients age and toxicities as reported elsewhere (48).
This study has revealed that amphotericin B dosage was an important predictor of its toxicity as similarly observed by Fischer et al., (38). The recommended dose of amphotericin B is 0.7mg/kg/day (11,12). But in this study all patients were given 50mg/day regardless of their weight. The mean weight of the participants was 55kg suggesting that some participants were receiving an overdose which could have predisposed such patients to toxicity. However, previous studies demonstrated that lipid formulations have reduced toxicity (40,46) although our study was not designed to demonstrate this as only deoxycholate form was used.

Pretreatment was an important aspect in the prevention of toxicity especially salt loading with normal saline has been demonstrated to decrease nephrotoxicity (51). In this study salt loading was a common practice and patients were given at least one liter of normal saline before amphotericin B infusion. Nevertheless, there was no statistical significant reduction in nephrotoxicity (p=0.881). Although analgesics were commonly administered followed by KCl as premedication, this did not seem to be important in preventing nephrotoxicity as demonstrated by Grasela et al (6) in a similar study. However, the clinicians in this study followed the treatment guidelines which recommend that a patient should be prehydrated with one liter of normal saline containing one ampoule of KCl (20) which was a common practice with 82.1% patients receiving the drugs. The intention was to prevent dehydration which is a risk factor for toxicity (38).

Baseline haemoglobin, potassium and serum creatinine were routinely done with over 70% of the patients having been monitored. According to the 2013 update guidelines for prevention, diagnosis and management of Cryptococcal Meningitis guidelines, haemoglobin should be monitored twice in the course of the treatment for every patient and potassium and serum creatinine should be monitored four times during the course of treatment (38). In this study, haemoglobin was monitored twice in only 3.8% of the patients, while potassium and serum creatinine were monitored twice. This contrasted the guidelines despite being important predictors of nephrotoxicity as reported in this study results. In addition, monitoring of fluid, potassium, creatinine and BUN is important to prevent nephrotoxicity as revealed in this study.

A high mortality at 37% is reported in this study which closely relates to other studies done in Kenya (20) However, CDC reports a higher mortality of 50-70% (19).
5.2: Limitations
As common with many retrospective studies:

1. Some of the files that were used for data collection were incomplete, had missing information and some were illegible.

2. The study was a retrospective in nature and verification of the accuracy of documented information was not possible.

3. Infusion rate and infusion time were not indicated regularly in patient files to assist in assessing their role in toxicity.

5.3: Conclusion
There was almost equal proportion of males and females. The most common concomitant drug was cotrimoxazole and TB was the most common comorbidity. Dosage of amphotericin B was an important predictor of toxicity. Prehydration with normal saline decreased nephrotoxicity. In addition, monitoring of potassium, blood urea nitrogen, serum creatinine and fluid was important in preventing toxicities of amphotericin B. Pretreatments with KCl, normal saline, analgesics did not prevent toxicity.

5.3: Recommendation
For practice

1) Previous studies have shown that amphotericin B infusion rate is an important parameter in preventing toxicity. We suggest future studies on the role of amphotericin B infusion rates in prevention of toxicities so as to inform on practice changes.

2) Monitoring of fluid, potassium and serum creatinine should be done routinely as recommended to assist in early detection of nephrotoxicity.

Recommendations for policy

1) The high mortality of 37% indicates the need to review the adherence to Cryptococcal Meningitis management guidelines in KDH.

2) Health workers should be sensitized on rational use of amphotericin B to reduce the toxicity. This is so particularly in per weight dosing and monitoring.
3) Further research is needed to compare the toxicity of the two formulations (liposomal and deoxycholate) of amphotericin B. In this study, only deoxycholate formulation was used. It was therefore not possible to determine the role of different formulations in toxicity profiles of amphotericin B available in Kenya.

References


APPENDICES

Appendix 1: Eligibility criteria assessment form

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Yes=1 No=2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18 years and over</td>
<td></td>
</tr>
<tr>
<td>HIV positive</td>
<td></td>
</tr>
<tr>
<td>Cryptococcal meningitis infection</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 2: Data collection form

Assessment of Toxicities Associated with amphotericin-B Administration among HIV Infected Adults with Cryptococcal Meningitis at Kiambu District Hospital

1. **Patient demographics**

   Study serial number………………………………..date [dd/mm/yy]………………..

   1.1) Age (years)……………….
1.2) Weight (kg) ............

1.3) Sex ................. 1[ ] male, 2 [ ] female

1.4) Marital status .......... 1 [ ] married 2[ ] single, 3[ ] divorced, 4[ ] separated 5 widowed [ ]

1.5) Employment status .......... 1[ ] employed, 2 [ ] self employed, 3[ ] un employed

1.6) Religion ......................... 1[ ] Christian, 2[ ] Muslims, 3[ ] others

1.7) Education level ...... 1[ ] informal, 2 [ ] primary, 3[ ] secondary, 4[ ] college and above

2. Risk factors for amphotericin-B toxicity

2.1) Total daily dose of amphotericin B .......... mg

2.2) Concomitant drugs

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Specify Name</th>
<th>Daily dose (mg)</th>
<th>Duration of use (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.3) Comorbidities (list) and duration

1 ......................

2 ......................

3 ......................

4 ......................

2.4) Viral load ....................... Copies/mL
2.5) CD4 count………………………/mL
2.6) Formulation………1[ ] deoxycholate, 2[ ] liposomal
2.7) Infusion rate……………………mg/min
2.8) Test dose……………1[ ]yes, 2[ ] no
2.9) Infusion time……………hours

3. **Toxicity associated with amphotericin-B**

3.1) Infusion related

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Tick if present</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nausea/ vomiting</td>
<td></td>
</tr>
<tr>
<td>2. Fever</td>
<td></td>
</tr>
<tr>
<td>3. Chills</td>
<td></td>
</tr>
<tr>
<td>4. Headache</td>
<td></td>
</tr>
<tr>
<td>5. Thrombophlebitis</td>
<td></td>
</tr>
<tr>
<td>6. Hypotension</td>
<td></td>
</tr>
<tr>
<td>7. Anaemia</td>
<td></td>
</tr>
<tr>
<td>8. Hypertension</td>
<td></td>
</tr>
<tr>
<td>9. Others (specify)</td>
<td></td>
</tr>
</tbody>
</table>

3.2) Nephrotoxicity profiles

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Tick if present</th>
<th>Specify level/units</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hypokalemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Hypomagnesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Increased serum creatinine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Acute renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Other (specify)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.3) Outcome of toxicity
a. Resolved spontaneously…………
b. treated----
c. Death………
d. Stopped therapy……
e. Admission. Length of hospital stay in days--------
f. Other(specify)………………

4. Preventive Strategies

4.1) Monitoring

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Times monitored within the 14 day treatment</th>
<th>Baseline value</th>
<th>Value one</th>
<th>Value two</th>
<th>Value three</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Haemoglobin g/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Serum creatinine mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Potassium mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Magnesium mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Blood urea nitrogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4.2) Premedication

   a. Analgesics………1[ ] yes, 2[ ] no. specific type---------------
   b. Antihistamines………..1[ ] yes, 2[ ] no. specific type---------
   c. Steroid………………1 [ ] yes, 2[ ] no. specific type----------
   d. KCl…………………1 [ ] yes, 2[ ] no
   e. Others (specify)

4.3) a) Salt loading…………………1 [ ] yes, 2[ ] no 3. specific type-------- 4. amount
b) Fluid input and output monitoring ..........1[ ] yes, 2[ ] no

5) Outcome of disease treatment

   a. cured----
   b. Death........
   c. relapse
   d. Other(specify).............
Appendix 3: Letter of Approval by KNH ethics committee

UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
P O BOX 19676 Code 00020
Telephone: 2727200 Fax 2727200

Ref: KNH-ERCIA/62

Agnes Wambui
School of Pharmacy
Dept of Pharmacuetics and Pharmacy Practice
University of Nairobi

Dear Agnes

Research Proposal: Assessment of toxicities associated with amphotericin-B administration among HIV infected adults with cryptococcal meningitis at Kiambu District Hospital (P69/02/2015)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and approved your above proposal. The approval periods are 12th February 2015 to 11th February 2016.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.
b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.
c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.
d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.
e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (Attach a comprehensive progress report to support the renewal).
f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.
g) Submission of an executive summary report within 90 days upon completion of the study. This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.

For more details consult the KNH/UoN ERC website www.erc.uonbi.ac.ke

Protect to discover
Yours sincerely

PROF. W. L. CHINDIA
SECRETARY, KNH/UON-ERC

c.c. The Principal, College of Health Sciences, UoN
The Deputy Director CS, KNH
The Assistant Director, Health Information, KNH
The Chairperson, KNH/UON-ERC
The Dean, School of Pharmacy, UoN
The Chairman, Pharmaceutics and Pharmacy Practice, UoN
Supervisors: Dr. David G. Nyamu, Dr. Peter N. Karimi
Appendix 4: Letter of Approval by KDH

To the Medical Superintendent,
Kiambu District Hospital,
P.O. Box 493,
Kiambu.

Dear Sirs,

RE: Application for Conducting Research at KDH

I am humbly requesting permission to conduct my research at Kiambu District Hospital. My research topic is Assessment of Toxicity associated with Amphotericin-B administration among the infected adult with Cryptococcal meningitis at Kiambu District Hospital.

The proposal has been approved by the KU Ethics and Research Committee.

All efforts will be appreciated.

Regards,

Dr. August Wambebin

[Stamp: RECEIVED 13 MAR 2015, MED SUP]

[Stamp: 13/3/15]

[Stamp: 18/3/15]

Waive research fee
Applicant member of staff, study leave
### Appendix 5: List of Concomitant Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotrimoxazole</td>
<td>65</td>
<td>16.41%</td>
</tr>
<tr>
<td>Potassium chloride</td>
<td>40</td>
<td>10.10%</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>36</td>
<td>9.09%</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>26</td>
<td>6.57%</td>
</tr>
<tr>
<td>Benzypencilllin</td>
<td>23</td>
<td>5.81%</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>23</td>
<td>5.81%</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>20</td>
<td>5.05%</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>18</td>
<td>4.55%</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>15</td>
<td>3.79%</td>
</tr>
<tr>
<td>Efanirenz</td>
<td>15</td>
<td>3.79%</td>
</tr>
<tr>
<td>Plasil</td>
<td>15</td>
<td>3.79%</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>11</td>
<td>2.78%</td>
</tr>
<tr>
<td>RHZE</td>
<td>8</td>
<td>2.02%</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>7</td>
<td>1.77%</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>6</td>
<td>1.52%</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>6</td>
<td>2.00%</td>
</tr>
<tr>
<td>Ranferon</td>
<td>5</td>
<td>1.26%</td>
</tr>
<tr>
<td>Tramadol</td>
<td>5</td>
<td>1.26%</td>
</tr>
<tr>
<td>Floxapen</td>
<td>4</td>
<td>1.01%</td>
</tr>
<tr>
<td>Ibruprofen</td>
<td>4</td>
<td>1.01%</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>4</td>
<td>1.01%</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>3</td>
<td>0.76%</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>3</td>
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</tr>
<tr>
<td>Azi/3tz/nvp</td>
<td>2</td>
<td>0.51%</td>
</tr>
<tr>
<td>Buscopan</td>
<td>2</td>
<td>0.51%</td>
</tr>
<tr>
<td>Erythomycin</td>
<td>2</td>
<td>0.51%</td>
</tr>
<tr>
<td>Folic acid</td>
<td>2</td>
<td>0.51%</td>
</tr>
<tr>
<td>Gentamycin</td>
<td>2</td>
<td>0.51%</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>2</td>
<td>0.51%</td>
</tr>
<tr>
<td>Pyridoxine</td>
<td>2</td>
<td>0.51%</td>
</tr>
<tr>
<td>Tdf/3tv/efv</td>
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<td>0.51%</td>
</tr>
<tr>
<td>Abacavir</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Acyclovir</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Aldactore</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Alluvia</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Aminovidine</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Amoxilllin</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Medicine</td>
<td>Units</td>
<td>Percentage</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------</td>
<td>------------</td>
</tr>
<tr>
<td>Cefixime</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Ferrous sulphate</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>HAART</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Heparin</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Lasix</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Loperamide</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Nystatin</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Phenobarbitone</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Pyrizinamide</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td>Relcer gel</td>
<td>1</td>
<td>0.25%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>396</strong></td>
<td><strong>100.00%</strong></td>
</tr>
</tbody>
</table>