FEATURE ARTICLE:

Amphotericin B toxicities among HIV infected adults with Cryptococcal Meningitis in Kiambu District Hospital
CONTENTS

Editorial:
Substandard and Counterfeit Drugs; A Threat to Health

Amphotericin B toxicities among HIV infected adults with Cryptococcal Meningitis in Kiambu District Hospital

Impact of devolution on the trends of Paediatric Malaria Admissions and Mortality in Homa-Bay County, Kenya- An Interrupted Time Series Analysis

Evaluating Corchorus Olitorius Plant Mucilage in the formulation of Oro-Dispersible Paediatric Sildenafil tablets

Presence of Potentially Harmful Alcohol Excipients in Paediatric Medicine Dispensed in Nairobi

The Occurrence of Glucose 6 Phosphate Dehydrogenase Deficiency amongst Blood Donors at the Regional Blood Transfusion Centre- Mombasa, Kenya

Provider perspectives on the Strengths and Weaknesses of the Devolved Health Care in a Rural County in Kenya

Guidelines for Contributors

The Pharmaceutical Society of Kenya (PSK) is a representative organization that was formed enabling Pharmacists’ to employ their professional expertise in the care of patients.

Established in 1964, PSK has its roots in the Pharmaceutical Society of East Africa, which was registered in 1950. Since its formation, PSK continues to promote a common standard for professional conduct and code of ethics for its members, as well as advocate for the welfare of Pharmacists.
EDITORIAL

SUBSTANDARD AND COUNTERFEIT DRUGS; A THREAT TO HEALTH

Judy Asin & Nadia Butt

Globally the ever-present issues of substandard medicines remain a challenge. World Health Organization (WHO) defines substandard medicines as genuine medicines provided by the manufacturer which do not meet quality specifications set for them by national standards. Substandard medicines include products with poor physical characteristics (for example friable tablets), inadequate quantity of the active ingredients, poor dissolution or bioavailability profiles and those that are poorly packaged and/or labeled. Counterfeit medicines on the other hand can be described as medicines that are deliberately and fraudulently mislabeled with respect to identity or source. They may contain the wrong active ingredient or no active ingredient and are of lesser value than the genuine product. Substandard medicines are often produced by licensed manufacturers but counterfeits can be produced in backyards, small industries or even at home.

The Kenyan market is flooded with various generic medicines and it is not always indicative that the products still meet expected quality once they have been granted marketing authorization. Certain loopholes, particularly illegal importation of medicines via the country’s porous borders, allow substandard and counterfeit medicines to enter the drug supply chain. These defective medicines may be subject to illegal hawking and sale or may indeed find their way into the authorized supply chain. At their very best, these medicines are ineffective to the patient and at their very worst, they tend to cause harm to the patient, promote development of drug resistance and increase morbidity and mortality rates.

Pharmacy and Poison’s Board (PPB) is the national medicines regulatory authority in Kenya and together with the analytical arm of National Quality Control Laboratory (NQCL) and Drug Analysis and Research Unit (DARU) ensure that pharmaceutical products are actively regulated and comply with set specifications for safety and effectiveness. However, these bodies face major challenges in the bid to protect the public from substandard and counterfeit drugs. DARU reported that between 2001 and 2005, 10.7-55.4% of antibiotic medicines failed to meet quality specifications. This finding was probably linked to the emergence of resistance against commonly used antibiotics during this period. In the year 2000, DARU reported identification of Panadol® junior tablets that contained the wrong ingredient (aspirin instead of paracetamol) and faulty packaging.

Concerns about high healthcare costs have resulted in tremendous utilization of generic products. According to the United States Food and Drug administration (USFDA), generics should only be marketed if they are bioequivalent and pharmaceutically equivalent to the originator or original drug. The large numbers of generic products locally may hamper pharmacovigilance efforts allowing the infiltration of substandard and counterfeit medicines. Circulation of substandard drugs is encouraged by the fact that drugs manufactured for export are often not regulated to the same standard as those manufactured for domestic use. In developing countries there is an abundance of small-scale suppliers who may supply the substandard or counterfeit medicines.

Substandard medicines may pose various risks to the population. Product contamination can lead to toxicity and fatalities as highlighted by various cases in literature. In October 2004, a doctor working for Medicines Sans Frontier in Darfur reported that a local donation of ringer’s lactate was contaminated with fungal growth. The death of 86 children in Haiti in 1996 after ingestion of paracetamol that contained the anti-freeze diethylene glycol, which led to acute kidney failure in those who ingested it, is another grave example. Recently in Kenya, some batches of gentamycin injection were recalled as they were reported to cause adverse reaction of severe headaches. On the worldwide front, all valsartan medications formulated using drug from a Chinese manufacturer were recently recalled due to contamination of the active pharmaceutical ingredient with a carcinogenic impurity. The presence of suboptimal amounts of active pharmaceutical ingredient compromises the treatment causing progression of the disease, antimicrobial resistance, increased morbidity and mortality rates. A study done in Nigeria in 2001 found out that almost half of randomly samples antibiotics and antiparasitics did not comply with the pharmacopoeia limits, containing less amounts of the active pharmaceutical ingredient, thus posing and a threat of development of antimicrobial resistance and hence prolonged illness. The social and economic effects of substandard medicines cannot be ignored. The patient using these ineffective medicines may lose confidence in health care professionals including their physician and pharmacist and potentially modern medicine as a whole. These patients also suffer from economic losses occasioned by unsuccessful therapy and worsening illness. The spread of substandard medicines also has political ramifications, undermining the governments’ investments in health delivery systems and its credibility with respect to providing quality health care.

Constant surveillance of marketed medicines through infrastructure development and capacity building in the country would strengthen quality assurance. For instance, imported drugs should routinely be tested on arrival so as to ensure that commercially available drugs in the market conform with the pharmacopoeial standards.
Amphotericin B toxicities among HIV infected adults with Cryptococcal Meningitis in Kiambu District Hospital

A.W. Karita*, D.G. Nyamu*, P.N. Karimi**, S.C. Gitau

1University of Nairobi, College of Health Sciences, Department of Pharmaceutics & Pharmacy Practice, P.O Box 19676-00202, Nairobi, Kenya. Emails: P.N. Karimi- ndirang@yahoo.com, D.G.Nyamu-dgnyamu@gamil.com, A.W Karita-aggienjane@gmail.com.

2Kenyatta University, Department of Pharmacy and complementary/Alternative medicine, P.O Box 43844-00100, Nairobi, Kenya, email—gitaus2009@gmail.com

*Corresponding author

Abstract

Background: HIV infection is a worldwide epidemic with the highest prevalence in sub-Saharan Africa. This has increased the prevalence of cryptococcal meningitis which is a common AIDS-related opportunistic infection with a high rate of morbidity and mortality. Amphotericin B is the standard treatment for cryptococcal meningitis but its use is limited by toxicities resulting from a number of factors such as cumulative dosage and concomitant drugs. Published local studies on patterns of toxicities are 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 patients aged 18 years and over in Kiambu District Hospital.

Methodology: A cross-section design was used that involved review of patients’ records at Kiambu District Hospital medical records department between January 2010 to December 2014. One hundred and six files of HIV infected adults with cryptococcal meningitis and treated with amphotericin B were used. Data on amphotericin B toxicities, risk factors, and preventive strategies 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 IBM Statistical Package for Social Sciences Version 22.0 for analysis. Bivariate analysis using chi-square test and logistic regression were used to determine statistical significance at 0.05. P values that were equal or less the 0.05 were considered significant.

Results: Prevalence of infusion-related toxicities was high at 87.7%, with fever being the most common (58.1%). The overall prevalence of nephrotoxicity was at 27.4% but principally characterized by hypokalemia (41.4%) and elevated creatinine at 58.6%. Dosing of the drug was not weight based and higher amphotericin B doses were important risk factors for toxicity (p=0.045). Prevention of toxicities associated with amphotericin B involved monitoring of serum levels of potassium (p=0.028) and creatinine (p=0.019) as well as patients hydration status (p=0.026). Monitoring of toxicity was only prevalent (70%) at the initiation of therapy but declined to less than 20% in the course of treatment.

Conclusion and recommendation: Prevalence of toxicity of amphotericin B in Kiambu District Hospital was high and related to the dose given. Therefore, care should be taken when dosing the drug. In addition, frequent patient monitoring, adequate hydration, and premedication are key to preventing the toxicity and should be encouraged.

Keywords: Amphotericin B, Cryptococcal meningitis, HIV/AIDS, Toxicity

Introduction

Invasive cryptococcal infection is the second most common HIV/AIDS-related complication after tuberculosis and results in up to 20% of deaths [1]. Amphotericin B is the standard treatment for cryptococcal meningitis, but its use is limited by toxicity [2, 3, 4]. These toxicities include nausea, vomiting, fever, chills, headache, rigors, hypertension or hypotension, cardiac arrhythmias, and skin rashes [5].

Prolonged administration of the drug leads to nephrotoxicity which manifests as renal insufficiency, hypokalaemia, hypomagnesaemia, renal tubular acidosis and nephrocalcinosis [6, 7]. Nephrotoxicity can be reversible or irreversible particularly in patients given large cumulative doses above 5 grams. Studies have shown that reversible normocytic normochromic anaemia develops in most patients due to the direct suppressive effect on erythropoietin production [8].

The risk factors for toxicity include cumulative dosage and concomitant drugs and the consequences include increased morbidity, mortality, length of hospital stay and cost of seeking treatment [9].

Several strategies, including, using newer amphotericin B with lipid conjugate, premedication, and monitoring of electrolytes, have proved to be effective in preventing toxicities. Despite this, the Kenyan public hospitals still use the conventional amphotericin B deoxycholate which is
more toxic than the newer formulations. In addition, HIV/AIDS patients are prone to high pill burden which may result in drug interactions with amphotericin B. Published local studies on assessment of toxicities remain scanty and therefore, the study sought to quantify the magnitude of the problem in Kiambu District Hospital (KDH).

Methods

Before commencing the study, approval was sought and granted by Nairobi National Hospital – University of Nairobi Ethics and Research Committee (Ref KNH-ERC/A/62) and Kiambu District Hospital. This was done to ensure that the research was conducted according to the principles of ethics which are pertinent to a sound scientific study.

A cross section design was used and the target population was the files of adult HIV positive patients, with cryptococcal meningitis who were treated with Amphotericin B while admitted in the hospital. The sample size was determined using Fisher’s formula (10) and findings from a similar study [11]. A list of all cryptococcal meningitis cases starting from January 2010 to December 2014 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 those that satisfied the requirements were included. These were records of patients who were at least eighteen years old with a confirmed diagnosis of HIV/AIDS and cryptococcal meningitis. In addition, they were treated with Amphotericin B. A total of 106 files were selected. Data was collected using a semi-structured form where sociodemographic characteristics, risk factors, and preventive strategies were picked. The forms did not have patient identifiers but a unique code. Data were stored in a lockable cabinet and thereafter 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. Safety of the electronic data was ensured using a protected Microsoft Access 2013 database. To ensure accuracy, once entry was completed, the Principal Investigator compared the entered data with the hard copy forms. Safety of the electronic data was ensured using a password that was changed regularly and administration rights were restricted. The system was protected by keeping updated antivirus and software. It was also backed up every day on a hard disk.

All aspects of quality assurance were adhered to. A pilot study was conducted to determine the reliability of the data collection tool and any error noted was corrected. Appropriate documentation was maintained at all times. External validity was optimized using adequate sample size. To ensure confidentiality, patient files were kept under lock and key and the review of the records was done within the hospital. Patients’ names were not entered in the data collection form but instead, codes were used. The extracted data were safely stored and analyzed using descriptive and inferential statistics. The relationship between variables was determined at 0.05 level of significance using chi-square and logistic regression.

Results

The baseline characteristics of the study population are summarised in Table 1. The mean age of the study participants was 37.4 (SD±8.9) years. Most (54, 50.9%) of the patients were females and 55 (51.9%) were married. Thirty-three (56.5%) were unemployed and 11 (10.4%) had attained the secondary level of education. About half (53, 50%) of the population was aged between 18-35 years.

Table 1. Social demographic characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Category</th>
<th>Frequency (n)</th>
<th>Percent (%)</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>Age (years)</td>
<td>18-35</td>
<td>53</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>36-65</td>
<td>47</td>
<td>44.3</td>
</tr>
<tr>
<td></td>
<td>Above 65</td>
<td>1</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>Not indicated</td>
<td>5</td>
<td>4.7</td>
</tr>
<tr>
<td>Marital status</td>
<td>Single</td>
<td>22</td>
<td>20.8</td>
</tr>
<tr>
<td></td>
<td>Married</td>
<td>55</td>
<td>51.9</td>
</tr>
<tr>
<td></td>
<td>Separated</td>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Divorced</td>
<td>3</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Widowed</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Not indicated</td>
<td>21</td>
<td>19.8</td>
</tr>
<tr>
<td>Employment</td>
<td>Formal employment</td>
<td>11</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>Self-employed</td>
<td>16</td>
<td>15.1</td>
</tr>
<tr>
<td></td>
<td>Unemployed</td>
<td>35</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Not indicated</td>
<td>44</td>
<td>41.5</td>
</tr>
<tr>
<td>Religion</td>
<td>Christian</td>
<td>70</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>Not indicated</td>
<td>36</td>
<td>34</td>
</tr>
<tr>
<td>Education level</td>
<td>Informal</td>
<td>5</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>10</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>11</td>
<td>10.4</td>
</tr>
<tr>
<td></td>
<td>Tertiary</td>
<td>2</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>Not indicated</td>
<td>78</td>
<td>73.6</td>
</tr>
</tbody>
</table>

Amphotericin B toxicity was associated with concomitant drugs used. Antibiotics were most prevalent (84.9%) followed by antiretrovirals (42.5%) and analgesics (33%) (Figure 1). Among the antibiotics, cotrimoxazole was the most common followed by benzylpenicillin and chloramphenicol.

Figure 1. Concomitant drugs used by the patients

The most common comorbidity among the cases was tuberculosis (TB) with a prevalence of 56.8%, followed by pneumonia (20.5%), candidiasis (11.4%) and gastroenteritis (11.4%) (Figure 2). The other diseases were anaemia and herpes zoster, among others.
Figure 2. Types of comorbidities among the patients

The study found both infusion-related and renal toxicities (Figure 3). The most common infusion-related toxicities were fever at 58.5% followed by headache (49.1%), nausea and hypotension (25.5%).

Figure 3. Types of infusion-related toxicities

Most of the patients experienced more than one infusion-related toxicities (Table 2). Only 13 (12.3%) patients did not experience infusion-related toxicities. Thirty-two (30.2%) experienced two infusion-related toxicities. Overall infusion-related toxicities were experienced by 87.7% of the patients. The prevalence of nephrotoxicity was 27.4%, with most common manifestations being elevated serum creatinine and hypokalemia, at 58.6% and 41.4%, respectively.

Table 2. The frequency 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>

The factors that had a significant association with the development of nephrotoxicity were fluid, potassium, creatinine and blood urea nitrogen monitoring. Conversely, gender, salt, and potassium chloride loading did not have any statistically significant association with the development of nephrotoxicity (Table 3).

Table 3: A bivariate analysis of factors associated with nephrotoxicity

<table>
<thead>
<tr>
<th>Factor</th>
<th>Status</th>
<th>No Nephrotoxicity</th>
<th>Nephrotoxicity</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>36 (73.5)</td>
<td>13 (26.5)</td>
<td>0.082</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>47 (87)</td>
<td>7 (13)</td>
<td></td>
</tr>
<tr>
<td>Salt loading</td>
<td>No</td>
<td>15 (78.9)</td>
<td>4 (21.1)</td>
<td>0.881</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>70 (80.5)</td>
<td>17 (19.5)</td>
<td></td>
</tr>
<tr>
<td>Potassium chloride use</td>
<td>No</td>
<td>58 (82.9)</td>
<td>12 (17.1)</td>
<td>0.336</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>27 (75)</td>
<td>9 (25)</td>
<td></td>
</tr>
<tr>
<td>Fluid input and output</td>
<td>No</td>
<td>65 (87.8)</td>
<td>9 (12.2)</td>
<td>0.003*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>20 (62.5)</td>
<td>12 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Creatinine monitoring</td>
<td>No</td>
<td>63 (86.3)</td>
<td>10 (13.7)</td>
<td>0.19*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>22 (66.7)</td>
<td>11 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Potassium monitoring</td>
<td>No</td>
<td>65 (85.5)</td>
<td>11 (14.5)</td>
<td>0.028*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>20 (66.7)</td>
<td>10 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Blood urea nitrogen</td>
<td>No</td>
<td>62 (86.1)</td>
<td>10 (13.9)</td>
<td>0.026*</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>23 (67.6)</td>
<td>11 (32.4)</td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant relationship

A number of preventive strategies were employed to reduce amphotericin B toxicities. The most common pretreatments were salt loading (82.1%) followed by analgesics (45.3%), potassium chloride (34%), steroids (3%) and antihistamines (1%). Additionally, monitoring of haemoglobin, creatinine, potassium, and Blood Urea Nitrogen (BUN) was done in over 70% of cases before administration of the drug. Nonetheless, the parameters were rarely monitored during the course of the treatment. Haemoglobin was monitored twice in twenty (18.9%) patients and thrice among four (3.8%). Creatinine was monitored once in 70.0% of the cases and twice in thirteen (12.3%) of them during the 14-day treatment. The frequency of patients monitoring decreased over time in the course of treatment. Fluid input and output monitoring were done in 30.2% of the cases. The majority (62.9%) of the cases recovered and the rest died. Most (33%) of the amphotericin B toxicities required treatment, while 22% resolved spontaneously. Death due to toxicity was reported in 13% while only 1% were discontinued and substituted with fluconazole.

A bivariate analysis between age and outcome of therapy found no significant association (p = 0.379). The only predictor for infusion-related toxicity was the 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. A logistic regression analysis found that fluids monitoring and potassium levels were independent factors associated with the 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) and those 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).
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 carried out at KNH showed similar results [11]. 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 among the HIV infected patients such as Pneumocystis jiroveci pneumonia, toxoplasmosis, and many bacterial infections. Tuberculosis was the most prevalent comorbidity as found elsewhere probably because it is common opportunistic infections in HIV infected patients [11]. The use of cotrimoxazole was followed by a combination of benzyl penicillin and chloramphenicol since before diagnosis the patients were being treated empirically for bacterial meningitis. Our results indicated that the infusion-related toxicity prevalence was high at 87.7% and fever was the most common followed by a headache. This compares favorably to previous studies that displayed toxicities prevalence of 71% with the most common being fever, chills, nausea, and headache [12, 13, 14]. Our study findings showed the prevalence of nephrotoxicity at 27.4% unlike in a previous study carried out at KNH by Ochieng et al., which showed its prevalence at 70.1% [23]. The difference in the results was probably because of erratic monitoring of adverse effects. There was no statistically significant relationship between patients’ age and toxicities as revealed elsewhere [15].

Our results revealed that amphotericin B dosage was an important predictor of its toxicity as also observed by Fischer et al. [16]. The recommended dose of Amphotericin B is 0.7mg/kg/day [17,18]. From our finding 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 leading to toxicity. [19, 20].

Pretreatment was an important aspect in the prevention of toxicity and salt loading with normal saline has been demonstrated to decrease nephrotoxicity [21]. In our study, this was a common practice and patients were given at least one liter of normal saline before Amphotericin B infusion. Nevertheless, there was no statistically significant reduction in nephrotoxicity.

Although analgesics were commonly administered followed by potassium chloride as premedication, this did not seem to be important in preventing nephrotoxicity as demonstrated in a similar study [12]. However, the clinicians followed the guidelines, which recommend that a patient should be prehydrated with one liter of normal saline containing one ampoule of potassium chloride [22] 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 [16]. Baseline haemoglobin, potassium and serum creatinine were routinely done with over 70% of the patients having been monitored. According to the 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 [16]. 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 according to our results.

The study revealed a high mortality of 37%, which closely relates to similar findings [22]. However, Centre for Disease Control reports a higher mortality of 50-70% [19]. The high mortality could be due to a combination of factors such as Cryptococcal Meningitis (CM), drug toxicity or other comorbidities.

In conclusion, the prevalence of toxicity in Kiambu District Hospital was high. Since amphotericin B dosage is an important predictor of toxicity it is recommended that caution should be taken when dosing. In addition, patient monitoring, hydration, and premedication are key in preventing the toxicity and should be encouraged.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgment

The authors acknowledge the staff of Kiambu District Hospital for allowing the researchers access the patients’ hospital records.

References


Impact of devolution on the trends of Paediatric Malaria Admissions and Mortality in Homa-Bay County, Kenya- An Interrupted Time Series Analysis

Kodhiambo M.O.1*, Amugune B.K.2 and Oyugi J.O.3

1Department of Pharmacy and Complementary/Alternative Medicine, Kenyatta University, P.O. Box 43844-00100, Nairobi, Kenya., Cell Phone:+254724468162, Email: kodhiambo.maurice@ku.ac.ke

2Department of Pharmaceutical Chemistry, University of Nairobi, Kenya

3Department of Medical Microbiology, University of Nairobi, Kenya.

*Corresponding Author

Abstract

Background: Malaria is a leading cause of paediatric admissions, morbidity and mortality. Its burden is borne mainly in the endemic areas, like Homa-Bay in Kenya, which are also the resource constrained regions. It is therefore important for the County to prioritize preventing paediatric malaria. Paediatric malaria admission and mortality have

Vol. 23, No 4/ Pharmaceutical Journal of Kenya / 2018
recently increased in the lake region unlike the rest of Kenya. It is also not clear whether after devolution was implemented in the year 2013, the trend has changed. The objective of the study was to investigate the impact of devolution on paediatric malaria admission and mortality trends in public health facilities in Homa Bay County.

Methodology: A retrospective quasi-experimental study was performed. The study population comprised all public health facilities in Homa Bay County. We purposively sampled 164 public health facilities from which six-year data on paediatric admissions and mortality was collected. Sub-County level data was obtained on excel from the electronic health records at the County headquarters. Hard copy data from the health facilities were also inspected at the 8 sub-Counties. Data was analyzed by the Interrupted Time Series (ITS) method. Devolution, which was taken as the intervention, occurred around the 36th month of the follow-up period in the year 2016.

Results: From January 2013, deaths increased gradually until around the 33rd month when it rose abruptly to nearly 800 then declined to below 200 in the 34th month around the time of devolution. This was followed by a period of stability. Admissions had a similar trend.

Conclusions and recommendations: Paediatric malaria admission and mortality rates in Homa Bay increased around the time of devolution. More studies are necessary to assess progress towards universal access to care post devolution.

Keywords: Devolution, paediatric malaria, admissions, mortality, Homa-Bay.

Introduction

Malaria is a protozoal disease prevalent mostly in the tropics and sub-tropics. Children of ages 5 years and below are the most vulnerable to malaria. The socio-economic burden of Malaria is greatest in the endemic areas of Kenya such as the Lake Victoria region. Devolution of health care was introduced in Kenya in the year 2013 to attempt to increase access to health care. This new system of government which was aimed at taking services closer to the people was put in place after the general elections of March 2013. Health care is among the functions of government that was devolved. The national government formulate health policy whereas the county governments are responsible for health service provision. The need to assess the impact of devolution especially in the marginalized and far flung counties like Homa Bay County is immense. Since the advent of devolution, health care providers have consistently resisted it. Initially, the resistance was seen in practising professionals, but empirical research has documented similar sentiments from students as well [1]. Most of them look forward to working in the private sector upon graduating. The public health managers in the county governments complain of poor work environment, transition challenges, restricted decision space, resource constrains and uncertainty among other challenges in rolling out devolution of health care services [2]. The typical bottlenecks for progress of devolution often involve lack of clear policies, poor transition processes and human resource malpractices [4, 5, 6]. On the other hand, the main aim of devolving health care was to improve access. Studies from Cote D’Ivoire [7, 8] and Kenya have shown that devolution may lead to equity and edging towards universal health coverage [9, 10]. This is because it removes barriers to care [11] and improves ownership and public participation in health care decisions [12, 13, 14]. For devolution of health to succeed, it is important to understand the needs of stakeholders such as the user communities, political leaders and health care providers [15, 16, 17].

Africa has in the recent past recorded varying trends in paediatric malaria admissions from country to country and between health facilities [18]. Even though overall paediatric malaria admission rate has been on the decrease in Kenya, that in the Kenyan lake region are on an upward trend [19]. In Malawi, the trend is similarly of an increase in admissions despite interventions aimed at reducing transmission such increased insecticide treated nets (ITN) coverage [18]. Around the same time when Artemisinin combination therapy (ACT) antimalarial drugs had been made to be first line, Uganda also recorded a significant increase in paediatric malaria admission rates [19]. Mortality rates due to paediatric malaria were also on an increasing trend despite a decrease in the number of microscopically confirmed cases. These trends seemed to correlate with the trends in ITN use, ACT stock levels and rainfall intensity [20]. Similar trends were recorded in Ethiopia [21], Malawi [20], Rwanda [20] and Ghana [22]. In the year 2016, even though malaria cases, admissions and deaths declined significantly, all cause admissions, all cause deaths and non-malaria cases and admissions increased significantly, showing the need to combat childhood illnesses in an integrated manner [22]. There is a deficiency of studies interrogating health policy correlates and implications of these trends. It is also not clear whether in Kenya, with devolution, the trend has improved, worsened or remained the same. The purpose of this study was, therefore, to investigate the impact of devolution on paediatric malaria admission and mortality trends in public health facilities in Homa Bay County.

Methods

We performed a retrospective quasi-experimental study from January 2010 until December 2016 in Homa Bay County. The study involved analysis of county paediatric malaria admission and mortality records. This information was obtained by reviewing the county and sub-County health records. The study population consisted of all public health facilities in Homa-Bay County. Homa-Bay County currently has 164 public health facilities with one County Teaching and Referral Hospital, four County hospitals, seven Sub-County Hospitals, 38 Health Centers, 88 Dispensaries, 7
Voluntary Counselling and Testing (VCT) Centers and 73 privately owned health institutions. For the purposes of this study, a total of 164 public health facilities were included. The study adopted purposive sampling since all the health facilities which presented admission and mortality data to the sub-County and County aggregation centers were included in the study. Health facilities that started operating after 2012 were excluded from the study since they lacked adequate pre-devolution data. Data from the 164 public health facilities were analyzed. Ethical approval was obtained from the KNH/U.O.N-Ethics and Review Committee (Ref-P389/05/2016). Confidentiality was ensured by using password protection when mailing data. Hard copy data was kept under lock and key accessible to the investigator only. Data was obtained from the electronic records at the Homa-Bay County teaching and referral hospital after authorization by the County secretary for health and the head of County Health Management Information Systems. The data was obtained in an excel sheet which was sent to the e-mail of the investigator under password protection. Data was then inspected for completeness and those facilities that lacked adequate pre-devolution data were excluded from the study. The data so obtained was an aggregate of facility level monthly admission and mortality. For purposes of triangulation, hard copy data from the health facilities were also inspected at the 8 sub-Counties. Data was analyzed by the Interrupted Time Series (ITS) analytic model. This involved plotting monthly paediatric malaria admissions and mortality against time from January 2010 to December 2016, with devolution, being the intervention, occurring around the 36th month. The plot was then visually inspected to see if devolution had an impact on the indicators. Interrupted time series analysis is a special type of time series analysis where treatment/intervention occurs at a specific point and the series is broken up by the introduction of the intervention. If the treatment has a causal impact, the post-intervention series will have a different level or slope. This design was used to quantitatively scrutinize trends of paediatric malaria admissions and deaths three years prior to and three years after the roll out of devolution of health care services in Kenya.

**The Model:** The time series analysis was done based on the logistic regression model represented by the following equation.

\[ \hat{Y}_t = \beta_0 + \beta_1 \times \text{time} + \beta_2 \times \text{intervention} + \beta_3 \times \text{time after intervention} + \epsilon_t \]

Where: \( \hat{Y}_t \) is the outcome time indicates the number of quarters from the start of the series, \( \beta_0 \) estimates the base level of the outcome at the beginning of the series, \( \beta_1 \) estimates the base trend, i.e. the change in outcome per quarter in the pre-intervention segment, \( \beta_2 \) estimates the change in level in the post-intervention segment, \( \beta_3 \) estimates the change in trend in the post-intervention segment and \( \epsilon_t \) estimates the error. Intervention is a dummy variable taking the values 0 in the pre-intervention segment and 1 in the post-intervention segment. Time after intervention is 0 in the pre-intervention segment and counts the quarters in the post-intervention segment at time.

**Results**

**Descriptive data.** A total of 275,936 admissions and 10,239 deaths were included in our analysis. These deaths therefore represented 37.1% of all paediatric malaria admissions in the County during the period of study. The deaths before 2013 were treated as death before devolution while deaths after 2013 were treated as deaths after devolution. The same applied for admissions. The descriptive summary statistics are shown in table 1 and graphically presented in figures 1 and 2 below.

**Table 1.** Data on Admissions and Death Rate (%).

<table>
<thead>
<tr>
<th>Year</th>
<th>Admissions Mean</th>
<th>Total Admissions</th>
<th>Deaths Mean</th>
<th>Total Deaths</th>
<th>Proportion of deaths by admissions</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>2010</td>
<td>90</td>
<td>1,084</td>
<td>8</td>
<td>90</td>
<td>8.3</td>
<td>Before</td>
</tr>
<tr>
<td>2011</td>
<td>2,903</td>
<td>34,835</td>
<td>140</td>
<td>1,683</td>
<td>4.8</td>
<td>Before</td>
</tr>
<tr>
<td>2012</td>
<td>3,283</td>
<td>39,397</td>
<td>204</td>
<td>2,442</td>
<td>6.2</td>
<td>Before</td>
</tr>
<tr>
<td>2013</td>
<td>2,847</td>
<td>34,167</td>
<td>157</td>
<td>1,883</td>
<td>5.5</td>
<td>After</td>
</tr>
<tr>
<td>2014</td>
<td>2,056</td>
<td>24,668</td>
<td>183</td>
<td>2,190</td>
<td>8.9</td>
<td>After</td>
</tr>
<tr>
<td>2015</td>
<td>2,608</td>
<td>31,300</td>
<td>163</td>
<td>1,951</td>
<td>6.2</td>
<td>After</td>
</tr>
</tbody>
</table>

Table 1 is an aggregated summary of yearly admissions and deaths for three years before and three years after devolution. The single horizontal line above the year 2013 indicates the time when devolution of health services to the county governments was implemented, thus being the intervention in this natural experiment. The average proportion of deaths by admissions before devolution was 6.4% compared to 6.9% after devolution. This represented a slight increase in deaths per admission after devolution.

**Inferential data.** The data on paediatric malaria admissions and deaths were plotted against time in months. Trends of admissions and deaths were as captured in figure 1. The graph was generated by a logistic regression modelling technique coupled with an interrupted time series analytic model.

Figure 1 (Next Page) shows trends of paediatric malaria deaths and admissions per month. From month zero, January 2013, deaths increased gradually until around the 33rd month when it rose abruptly to nearly 800 and declined back to below 200 in the 34th month. This was then followed by a stable trend of deaths being around 180 per month. Admission data started from near zero at month zero, increased sharply to almost 1000 in month five then fell equally sharply to zero in month 10. From month 12, admissions rose drastically to above 4000, stabilized around 3800 up to month 40 then gradually declined to month 60 after which a gradual increase started.
experienced in Tanzania where health services were devolved earlier [23]. As was reported from a study in Nepal, other issues that may act as bottlenecks to achievement of benefits of devolution early enough may include poor coordination among different sectors, improper handover process, poor selection management committees and incoherent capacity building [24]. It is however prudent to note that determinants of disease incidence are often a complex combination of several interacting factors that may not be effectively studied retrospectively [17]. Moreover, managing specialized health services in a devolved health system is usually challenging [10]. At that time, as it is largely still to date, there was poor harmonization of terms of service, incentives and amenities available to health workers in remote areas like Homa Bay County [3]. This could have affected the morale of health care providers hence poor service delivery. The process of devolution is work in progress and by 2013, it was in its infancy stages. It has been noted that devolution plans are not often implemented as intended [8]. It is therefore likely that there were deviations in implementation of health care devolution in Kenya, thus leading to unintended outcomes like has been observed in this study.

Discussion

The admissions increased from 2010 and stabilized around 2013. This abrupt rise was around the 36th month when devolution of health care was implemented. This was followed by a gradual decline in which again stabilized around 2014. The increase in the admissions may be attributed to anticipation of better services given that devolution of other services had begun by 2011. The people's perceptions may have improved in the backdrop of impending devolution of health services. The message that was given to citizens during the campaigns for the new constitution was that with devolution, they would participate more in making decisions about their health thus improving access and quality of health they would receive. In the year 2001, residents of Saskatchewan reported a similar experience. Most of them felt that devolution had resulted in greater local control and better quality of health care decisions [13]. Having been promulgated in the year 2010 August 27th, the new constitution seems to have given the citizens of Homa Bay County a new hope of better health services in their public health facilities. On the other hand, deaths seemed to have declined between 2010 and 2011, stabilized until 2013 after which there was a sharp increase. The possible explanation for this observation is that given the increase of admissions around the year 2013 when devolution was implemented, the number of deaths would be expected to similarly increase merely due to increase in the number of sick children admitted to the hospitals. Alternatively, there is a possibility that admissions and deaths increased due to better health records management after devolution. If the increasing trend of deaths reflected a genuine pattern, then this may be attributed to many factors including the fact that most health facilities were not properly prepared for the intricate realities of devolving health care and hence were struggling with management of health service delivery in the new context of devolution [2,5]. Autonomy of the County health care resource management was also not yet adequate. For example, a lot of money was being used to upgrade the infrastructure of small facilities to higher level hospitals. Such challenges were

Conclusion and Recommendations

These findings provide evidence that devolution of healthcare still has erratic and fluctuating outcomes with specific reference to paediatric malaria admissions and deaths in Kenya. In general, devolution seemed to have increased paediatric admission and mortality rates in Homa Bay over the period of the study. More studies need to be conducted in many Counties in Kenya to visualize the real impact of devolution on our health care service delivery. A study focusing on facility level analysis of paediatric malaria indicator data would be useful to unearth any trends unique to each facility as well as trends across facility levels.

References


Evaluating *Corchorus Olitorius* Plant Mucilage in the formulation of Oro-Dispersible Paediatric Sildenafil tablets

Njoroge A. N.¹, Tirop L. J.²

1 Gilgil Sub-county Hospital, Nakuru County. Email:staceynn12@gmail.com

2 Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, University of Nairobi

*Corresponding author:

**Abstract**

Sildenafil Citrate (SC), used in management of pulmonary arterial hypertension, is available in adult tablet dosage forms, from which paediatric doses are prepared contemporaneously. Sildenafil citrate oro-dispersible tablets in paediatric strengths, made from *Corchorus olitorius* (jute) plant mucilage as the natural superdisintegrant, provides for a dose specific, more stable, cheap and convenient dosage form in this population.

Typically synthetic superdisintegrants, namely croscarmellose sodium, crospovidone and sodium starch glycolate, are used in the formulation of oro-dispersible tablets. This work aimed to formulate paediatric oro-dispersible tablets containing Sildenafil citrate, using mucilage of jute plant (*Corchorus olitorius*) as a novel natural superdisintegrant. The mucilage was successfully extracted with 96% ethanol and characterized, demonstrating favorable parameters for use as a tablet superdisintegrant. Twelve batches of Sildenafil oro-dispersible tablets were formulated by direct compression, at three levels of the novel superdisintegrant as well as the common synthetic superdisintegrants, and evaluated.

The *Corchorus olitorius* mucilage batches showed characteristic mean in-vitro dispersion times of 20.67, 19.33 and 18.67s for the 5 mgs, 7.5 mgs and 10 mgs (4%, 6%, 8% w/w) tablet concentrations, respectively. The in-vitro dispersion time of tablets containing *Corchorus olitorius* mucilage compared closely with that of tablets containing croscarmellose sodium and sodium starch glycolate. The in-vitro dispersion time was observed to decrease with increasing concentrations of the mucilage powder. The tablets complied with all compendial tests for quality with the exception of the friability test. *Corchorus olitorius* mucilage may be used safely at higher concentrations to achieve lower in-vitro dispersion times. Further studies to establish the optimum superdisintegrant concentration should be considered.

**Key words:** Oro-dispersible tablet, Sildenafil citrate, Superdisintegrant, *Corchorus olitorius* mucilage.

**Introduction**

Sildenafil citrate (SC), a phosphodiesterase 5 inhibitor, is a vasodilator used in the management of pulmonary arterial hypertension in both adults and children [1]. Sildenafil formulations available locally include regular and oro-dispersible tablets, in strengths of 25 mgs, 50 mgs and 100 mgs, for the treatment of erectile dysfunction in adult patients. However there is no dose specific formulation for paediatric patients necessitating extemporaneous modification, viz crushing of the adult tablets and mixing the resultant powder with diluents to form liquid dosage forms, which is tedious and error prone. The dosing recommendation for SC in management of acute pulmonary hypertension in children below 1 year is a starting dose of 0.25-0.5 mg/kg orally every 4 to 8 hours, and 2.5 mgs three times a day for those aged above 1 year, with a body weight less than 20 kg [2]. An oro-dispersible tablet (ODT) is a highly convenient dosage form that takes into consideration swallowing difficulties especially among paediatrics [3].

ODTs disintegrate in the mouth within seconds, thus easily swallowed in the absence of water, and very little or no residue is left upon being orally administered. ODTs provide rapid drug delivery with a rapid onset of action and increased bioavailability. There is potential pre-gastric absorption which eliminates pre-systemic metabolism of the drug [4]. Additionally, ODTs provide rapid drug delivery with a very fast onset of action and increased bioavailability [5,6]. Several conventional techniques for preparation of ODTs exist, which include: direct compression with use of superdisintegrants, lyophilisation, mass-extrusion spray-drying, nanonization, compaction, moulding and sublimation. Some patented technologies employing these techniques for formulation of various drugs include: Zydis®, Orasolv®, Durasolv® and Flashtab® [3].

Superdisintegrants, which are added in optimal concentrations to achieve rapid disintegration, exert their activity based on such mechanisms as swelling, porosity and capillary action (wicking). Superdisintegrants are broadly classified as synthetic and natural. The common synthetic superdisintegrants are croscarmellose sodium, crospovidone and sodium starch glycolate [6]. Direct compression with addition of superdisintegrants is an economical technique, as it employs conventional manufacturing equipment [7]. Natural superdisintegrants are cheaper, biocompatible and biodegradable hence eco-friendly, easily available, non-toxic and have no side-effects [8]. Natural superdisintegrants have, in some
cases, been shown to exhibit faster drug dissolution and improved bioavailability of the active pharmaceutical ingredient [9]. Indeed, various studies have demonstrated the superiority or equivalent superdisintegrant activity of natural superdisintegrants to synthetic ones. For instance, in their study on *Trigonella foenum-graceum* (fenugreek seed) Kumar R. et al. demonstrated that mucilage of fenugreek seeds showed better disintegration than synthetic superdisintegrants in ODTs of metformin [10]. Shirsand S.B. et al. showed that disintegration results obtained from *Plantago ovata* mucilage in formulation of prochlorperazine maleate, were comparable and slightly better than those of crospovidone [11].

*Corchorus olitorius* is a common indigenous leafy vegetable in Western Kenya popularly known as ‘mrenda’. It is grown all year round, has excellent disease and pest resistance and gives stable yields even under difficult climatic conditions. It can be harvested 3–4 weeks after planting and is a good source of proteins, vitamin A,C,E, and mineral nutrients like calcium and iron [12].

*Corchorus olitorius* was investigated as a potential source of a cheap, non-toxic and easily available natural superdisintegrant, owing to its mucilaginous nature, given that most natural superdisintegrants are sourced from plant mucilages and gums [13], for the formulation of oro-dispersible sildenafil tablets.

### Methods

The *Corchorus olitorius* plant material was collected by proxy, from Kakamega rainforest area in Western Kenya. The plant material was uprooted by the roots, packed in a clean sack which was sealed and transported by road.

![Figure 1. Image of the leaves of *Corchorus olitorius*](image)

All other materials, which were of pharmaceutical grade, were obtained from the School of Pharmacy, University of Nairobi and from collaborators.

**Extraction of mucilage:** The leaves of *Corchorus olitorius* were washed with water to remove any foreign material, dried at 50°C and milled using a cutter mill. 400 g of plant material was soaked in 2 litres of distilled water for 6 hours at 60°C with continuous stirring using a magnetic stirrer, until the mucilage was completely released into the water. Thereafter, the plant material was filtered using a modified muslin cloth. The mucilage was then flocculated by pre-extraction with 96% ethanol for duration of 24 hours at room temperature, recovered by washing with 3 volumes of acetone, followed by drying in an oven at 45°C. The dried mucilage was then grinded using a mortar and pestle and passed through sieve number 70. The powder was weighed and stored in a desiccator until use [14].

**Physicochemical characterization of the mucilage powder:** The extracted mucilage was evaluated for the organoleptic properties of taste, odor, color and texture. Iodine test was used for identification, by adding 1 ml of 0.2 N iodine solution to 100 mg of dried mucilage powder.

The swelling index was determined by placing one gram of the *Corchorus olitorius* mucilage powder in a 25 ml measuring cylinder, 25 ml of distilled water was then poured into the measuring cylinder and shaken thoroughly every 10 minutes for 1 hour. The mixture was left to stand for 24 hours and volume occupied by the mucilage powder noted. The swelling index (SI) was then calculated. To determine the loss on drying, one gram of *Corchorus olitorius* mucilage powder was accurately weighed and dried in a hot air oven at 105°C with the weight being checked at intervals of 10 min. When there was no further change in the weight of powder, the loss on drying was calculated. The pH of a 1% w/v aqueous solution of the *Corchorus olitorius* mucilage powder was determined using a digital pH meter. 1% w/v of the mucilage in water was prepared and its viscosity determined using a Cole-Parmer® rotational viscometer, spindle L2 and torque 50.8%. The solubility was determined by shaking the powdered mucilage in different solvents viz warm water, cold water, acetone, ethyl alcohol and chloroform. Mucilage size and shape was determined by optical microscopy, using a Nikon®, Japan, phase contrast microscope. Finally, the flow properties of the mucilage, were assessed by determination of tapped and bulk densities, to calculate Hausner’s ratio and Compressibility index.

**Pre-formulation studies on powder blends:** The powder blends of sildenafil citrate and excipients were prepared by obtaining the required amounts of pure drug and excipients for every formulation, which were ground to fineness and mixed. The blends were evaluated for flow properties as described for mucilage powder above.

Drug excipient compatibility studies of the drug excipient blends in 1:1 ratio, was carried out using FTIR spectroscopy over the range of 4000 to 600 cm⁻¹. Samples were subjected to FTIR immediately after mixing and the resultant scans used to establish any predictable incompatibilities.

**Formulation and evaluation of sildenafil citrate ODTs:** Twelve tablet batches comprising of three different concentrations (4%, 6%, 8% w/w) of a superdisintegrant, *Corchorus olitorius* mucilage, croscarmellose, crospovidone or sodium starch glycolate, were prepared (Table 1). Other tablet excipients used included mannitol (filler), microcrystalline cellulose (binder), colloidal silicon dioxide (glidant), magnesium stearate (lubricant), sodium saccharin (sweetener) and strawberry flavor. All ingredients were ground individually using a pestle and mortar then passed through sieve number 60 separately to ensure ideal particle
size was achieved. The required quantities of the various ingredients were weighed and mixed uniformly in a mortar for 10 minutes, with the exception of magnesium stearate, which was added last and mixed with the rest of the blend for a further 3 minutes. The powder blends were then compressed into 125 mg tablets with each batch comprising of one hundred tablets. The amount of sildenafil citrate in each tablet was 2.5mgs.

**Table 1.** Master formula for the preparation of sildenafil citrate oro-dispersible tablets (quantities in mgs)

<table>
<thead>
<tr>
<th>Batch</th>
<th>Sildenafil citrate</th>
<th>Mannitol</th>
<th>Corscholar alitorus mucilage</th>
<th>Cross-carmellose</th>
<th>Cross-potone</th>
<th>Sodium starch gylcolate</th>
<th>Micro crystalline cellulose</th>
<th>Colloidal silicon dioxide</th>
<th>Magnesium stearate</th>
<th>Sodium saccharin</th>
<th>Strawberry flavor</th>
<th>Total Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC01</td>
<td>2.5</td>
<td>73.5</td>
<td>5.0</td>
<td>-</td>
<td>-</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>SC02</td>
<td>2.5</td>
<td>71.0</td>
<td>7.5</td>
<td>-</td>
<td>-</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>SC03</td>
<td>2.5</td>
<td>68.5</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>SC04</td>
<td>2.5</td>
<td>73.5</td>
<td>-</td>
<td>5.0</td>
<td>-</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>SC05</td>
<td>2.5</td>
<td>71.0</td>
<td>-</td>
<td>7.5</td>
<td>-</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>SC06</td>
<td>2.5</td>
<td>68.5</td>
<td>-</td>
<td>10</td>
<td>-</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>SC07</td>
<td>2.5</td>
<td>73.5</td>
<td>-</td>
<td>-</td>
<td>5.0</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>SC08</td>
<td>2.5</td>
<td>71.0</td>
<td>-</td>
<td>-</td>
<td>7.5</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>SC09</td>
<td>2.5</td>
<td>68.5</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>SC10</td>
<td>2.5</td>
<td>73.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>1.0</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>SC11</td>
<td>2.5</td>
<td>71.0</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.5</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.0</td>
<td>125</td>
<td></td>
</tr>
<tr>
<td>SC12</td>
<td>2.5</td>
<td>68.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>10</td>
<td>37.5</td>
<td>1.5</td>
<td>1.5</td>
<td>2.5</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

The tablets were then evaluated for weight variation, hardness, thickness, friability, assay and content uniformity as per USP guidelines. They were also assessed for wetting time, water absorption ratio and in-vitro dispersion time as described by Naazia and Neeharika [15].

**Results and Discussion**

**Physicochemical characterisation of mucilage powder**

The mucilage yield was 7% w/w, which was quite significant, given the anticipated small quantity needed as a tablet superdisintegrant. The organoleptic characteristics of the mucilage are an ash brown powder with a mucilaginous (mucourish) taste, fine texture and characteristic smell. No color change was observed in the iodine test, indicating the absence of starch. Mucilage is a fine texture and slightly soluble in cold water, acetone and ethyl alcohol and insoluble in non-polar chloroform. This solubility pattern indicates that the mucilage is quite polar. The particle size range obtained by light microscopy was 1-4 μm. The particles were sub-spherical or irregular in shape, light brown in color and singly distributed with a puffy appearance. An angle of repose of 36.4° was obtained, indicating fair flow properties. Hausner’s ratio and compressibility index range of 20.8% to 25%, thus acceptable for tablet manufacture.

**Preliminary formulation studies on powder blends**

The FTIR scans of the freshly mixed powder blends revealed no predictable drug excipient incompatibilities. FTIR studies of powder blends after storage under different conditions were not performed due to time constraints. The powder blends exhibited fair and passable flow properties, with Hausner’s ratio in the range of 1.25-1.33 and Compressibility index range of 20.8% to 25%, thus acceptable for tablet manufacture.

**Evaluation of tablets**

The results for evaluation of tablets are presented in Table 2.

**Weight variation:** All the tablet batches passed the weight uniformity test; whereby not more than two tablets intra-batch varied from the average tablet weight by ±7.5 % deviation.

**Assay:** All tablet batches except SC01 and SC07 were within the compendial limits of 90%-110% for low dose formulations. The slightly low API content in these two tablet batches out of the twelve batches may have resulted from non-homogenous mixing of the API with the other excipients.

**Content uniformity:** All tablet batches conformed to compendia specifications, where the relative standard deviation (RSD) should be less than 6% and no value is outside 85-115%.

**Hardness, thickness and friability:** The hardness values obtained were variable and seemingly dependent on the compression pressure which was varied manually, in-process, to attain a hardness of 10-35N ideal for ODTs. The friability (limit <1%) attained could not guarantee robust tablets, a common challenge with ODTs. ODTs are usually fragile due to their low mechanical strengths and the hygroscopic nature of the superdisintegrants. Furthermore the tablet thickness of 1.2mm, contributed to the friable nature of the tablets.
**Wetting time and water absorption ratio:** These measurements were carried out in pH 6.8 phosphate buffer at a temperature of 37±0.5o to simulate the conditions of saliva. Tablets comprising crospovidone superdisintegrant displayed shortest wetting times and lowest water absorption ratios.

**In-vitro dispersion time:** The in-vitro dispersion time, carried out in pH 6.8 phosphate buffer at a temperature of 37±0.5o to simulate the conditions of saliva, was used as a modified disintegration test due to the very short disintegration times involved. The end point for complete disintegration is the state whereby any residue that remains is a soft mass, having no palpable firm core.

All batches met the FDA specification for ODTs, of disintegration time < 30 seconds. A direct relationship between the wetting time and water absorption ratio to the in-vitro dispersion time was observed across the batches. Dispersion time decreased with an increase in the concentration of mucilage. Disintegration is achieved by swelling from the edges, very rapid initially, but rather slow at the end due to formation of gel coat that slows water movement to the remaining tablet core. The dispersion time of the SC tablets containing Corchorus olitorius mucilage compared closely with that of tablets containing croscarmellose sodium and sodium starch glycolate. The in-vitro dispersion time was observed to decrease with increasing concentrations of the mucilage powder. The tablets complied with all compendial tests for quality with the exception of the friability test.

Corchorus olitorius mucilage has the advantage of being non-toxic, a nutritional supplement and eco-friendly. Higher concentrations can be safely used to achieve lower in-vitro dispersion times. Further work should be carried out to establish the optimum concentration of Corchorus olitorius mucilage powder, for its superdisintegrant activity. Subsequently, stability studies on the optimized tablets should be performed.

### References

4. Deshmukh B, Narkhede K, Chaudhari P. Formulation and In Vitro evaluation of fast dissolving tablet

### Table 2. Evaluation of the sildenafil citrate oro-dispersible tablets

<table>
<thead>
<tr>
<th>Batch</th>
<th>Weight (mgs)</th>
<th>Hardness (N)</th>
<th>Thickness (mm)</th>
<th>Friability (%)</th>
<th>Wetting time (s)</th>
<th>Water absorption ratio</th>
<th>Dispersion time (s)</th>
<th>Assay (%)</th>
<th>Content uniformity (% ± RSD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC01</td>
<td>132 ± 4.62</td>
<td>23.80 ± 3.25</td>
<td>1.3 ± 0.06</td>
<td>4.47</td>
<td>5.67 ± 0.58</td>
<td>4.91 ± 1.79</td>
<td>20.67 ± 1.15</td>
<td>82.4 ± 8.79</td>
<td>100 ± 0.10</td>
</tr>
<tr>
<td>SC02</td>
<td>129 ± 4.20</td>
<td>15.33 ± 9.61</td>
<td>1.3 ± 0.06</td>
<td>6.30</td>
<td>5.69 ± 1.15</td>
<td>7.61 ± 2.60</td>
<td>19.33 ± 1.15</td>
<td>92.9 ± 5.92</td>
<td>100 ± 0.05</td>
</tr>
<tr>
<td>SC03</td>
<td>129 ± 4.68</td>
<td>9.67 ± 2.34</td>
<td>1.2 ± 0.00</td>
<td>10.89</td>
<td>5.33 ± 0.58</td>
<td>5.42 ± 1.42</td>
<td>18.67 ± 1.15</td>
<td>92.0 ± 5.11</td>
<td>100 ± 0.11</td>
</tr>
<tr>
<td>SC04</td>
<td>132 ± 6.06</td>
<td>3.20 ± 2.28</td>
<td>1.3 ± 0.06</td>
<td>1.79</td>
<td>5.33 ± 0.58</td>
<td>2.17 ± 0.89</td>
<td>19.33 ± 1.15</td>
<td>92.9 ± 2.60</td>
<td>100 ± 0.10</td>
</tr>
<tr>
<td>SC05</td>
<td>136 ± 8.03</td>
<td>30.30 ± 7.53</td>
<td>1.2 ± 0.00</td>
<td>2.16</td>
<td>13.67 ± 0.58</td>
<td>4.84 ± 1.59</td>
<td>25.67 ± 0.58</td>
<td>101.1 ± 6.52</td>
<td>100 ± 0.05</td>
</tr>
<tr>
<td>SC06</td>
<td>134 ± 5.49</td>
<td>24.40 ± 4.92</td>
<td>1.2 ± 0.06</td>
<td>8.29</td>
<td>13.00 ± 2.00</td>
<td>2.78 ± 0.29</td>
<td>24.33 ± 0.58</td>
<td>90.9 ± 1.21</td>
<td>100 ± 0.08</td>
</tr>
<tr>
<td>SC07</td>
<td>133 ± 3.79</td>
<td>30.20 ± 7.00</td>
<td>1.2 ± 0.00</td>
<td>1.52</td>
<td>2.00 ± 0.00</td>
<td>2.86 ± 2.29</td>
<td>4.33 ± 0.58</td>
<td>85.8 ± 3.35</td>
<td>100 ± 0.05</td>
</tr>
<tr>
<td>SC08</td>
<td>133 ± 4.27</td>
<td>30.00 ± 7.35</td>
<td>1.2 ± 0.00</td>
<td>1.71</td>
<td>2.00 ± 0.00</td>
<td>1.80 ± 0.95</td>
<td>6.33 ± 2.08</td>
<td>94.1 ± 2.86</td>
<td>100 ± 0.12</td>
</tr>
<tr>
<td>SC09</td>
<td>129 ± 3.07</td>
<td>31.00 ± 7.98</td>
<td>1.2 ± 0.00</td>
<td>1.40</td>
<td>2.00 ± 0.00</td>
<td>1.01 ± 0.27</td>
<td>4.00 ± 0.00</td>
<td>98.3 ± 12.44</td>
<td>100 ± 0.03</td>
</tr>
<tr>
<td>SC10</td>
<td>133 ± 6.23</td>
<td>13.00 ± 6.16</td>
<td>1.3 ± 0.06</td>
<td>7.60</td>
<td>15.67 ± 2.52</td>
<td>3.22 ± 0.48</td>
<td>20.00 ± 1.00</td>
<td>93.3 ± 2.50</td>
<td>100 ± 0.05</td>
</tr>
<tr>
<td>SC11</td>
<td>130 ± 5.46</td>
<td>15.6 ± 5.18</td>
<td>1.1 ± 0.06</td>
<td>4.96</td>
<td>15.00 ± 3.00</td>
<td>4.39 ± 2.42</td>
<td>17.00 ± 1.00</td>
<td>106.2 ± 2.59</td>
<td>100 ± 0.05</td>
</tr>
<tr>
<td>SC12</td>
<td>135 ± 8.37</td>
<td>16.4 ± 6.23</td>
<td>1.3 ± 0.06</td>
<td>2.95</td>
<td>15.30 ± 2.00</td>
<td>1.42 ± 0.23</td>
<td>17.67 ± 1.15</td>
<td>101 ± 3.15</td>
<td>100 ± 0.07</td>
</tr>
</tbody>
</table>

### Conclusion and Recommendation

Mucilage powder of Corchorus olitorius leaves was successfully extracted and characterised. The mucilage was deemed suitable for tablet manufacture as a superdisintegrant, owing to its high swelling index of 85.7%. Powder flow characterization on all tablet powder blends predicted passable flow character. Direct compression, using mannitol as the filler, was used to formulate the sildenafil citrate tablets. Each of the four superdisintegrants, Corchorus olitorius mucilage powder, croscarmellose, crospovidone and sodium starch glycolate was incorporated at 5 mgs, 7.5 mgs and 1 gms (4%, 6%, 8% w/w) concentrations to make a total of twelve tablet batches.

Post-compression tests demonstrated that tablets had a good distribution of the API and low in-vitro dispersion times of <30 s. The in-vitro dispersion time of tablets containing Corchorus olitorius mucilage compared closely with that of tablets containing croscarmellose sodium and sodium starch glycolate. The in-vitro dispersion time was observed to decrease with increasing concentrations of the mucilage powder. The tablets complied with all compendial tests for quality with the exception of the friability test.


Presence of Potentially Harmful Alcohol Excipients in Paediatric Medicine Dispensed in Nairobi

Maureen W Chege¹, Sylvia A Opanga²*

¹Muranga County Hospital, Kenya.
²School of Pharmacy, University of Nairobi, Kenya. sylvia.adisa@gmail.com sopanga@uonbi.ac.ke
*Corresponding Author

Abstract

Background: Alcohol, as an excipient in pharmaceutical preparations, serves as a preservative and solvent. It is commonly found in oral and topical formulations, elixirs and spirits. Although it has been widely used in paediatric formulations, its safety in children has not been well characterized though toxicity has been reported.

Objective: The aim of the study was to document the presence and content of alcohol excipients in paediatric drug products dispensed in pharmacies in Nairobi.

Methods: A cross sectional study was conducted at seven randomly selected pharmacies in Nairobi. The investigators selected all paediatric products and perused their packages, labels and package inserts for information on presence of alcohol, content, type of alcohol excipients and recommendations for use. The data was entered into Microsoft Excel 2010 worksheet, and descriptively analysed.

Results: Out of 290 products sampled, 87 (30%) were found to have alcohol excipients. Ethanol was the most common type of excipient (46.0%), followed by propylene glycol (27.6%). Syrups had the highest number of products with alcohol (58.6%). Antihistamines recorded the highest number of products with alcohol (39.1%). Most of the products with alcohol were over the counter drugs (79.3%). Of the drugs that contained alcohol, 53% (n=46) were not recommended for use by patients less than 6 years of age. The daily dose of alcohol in the drug with the highest alcohol content was equivalent to 28.8 ml of beer.

Conclusion: Over the counter drugs had more products containing alcohol than the prescription only drugs. Ethanol and propylene glycol were the most commonly used excipients. The propylene glycol content was not stated in all its products. The highest amount of alcohol per daily dose of drugs was equivalent to 28.8 ml of beer. Nearly half of the products were not recommended for children less than 6 years old.
Key words: Paediatric medicine; Alcohol; Ethanol; Excipient; Propylene glycol

Introduction

Pharmaceutical excipients are substances that are included in a pharmaceutical dosage form not for their direct therapeutic action, but to aid the manufacturing process, to protect, support or enhance stability, or for bioavailability or patient acceptability [1]. Ideally, an excipient is pharmacologically inactive, non-toxic, and does not interact with the active ingredients or other excipients. However, in practice few excipients meet these criteria. Toxicity may relate to compounds used as excipients in the final dosage form or to residues of compounds (such as solvents) used during the manufacturing process. [2]

The excipients to be used in formulations for the paediatric population should be selected with special care, taking into consideration the differences in the paediatric age group and maturity of organ systems [3]. Despite this, many paediatric preparations that were licensed prior to the new European Union paediatric regulation contain excipients that are no longer recommended for use in children. Besides this, the available safety data for excipients are often extrapolated from adult data, which makes it difficult to characterise the safety and toxicity profiles specific to paediatrics [3].

The paediatric population is particularly vulnerable to adverse reactions owing to organ immaturity and differences in pharmacokinetic and pharmacodynamic profiles compared with adults [4]. The toxicity of excipients may differ across the paediatric subsets. Children, especially the younger age groups, may require age-appropriate formulations, which sometimes have to be compounded within hospitals, without guidelines on excipient content. Use of certain excipients which contain alcohol may be harmful and may lead to effects such as neurological dysfunction [5]. Use of combinations of drugs with alcohol excipients in children, especially over the counter drugs, further increases the chances of toxicity [6].

Different types of alcohol are used as excipients in different drug formulations. These include: ethanol, benzyl alcohol and propylene glycol. Ethanol is widely used as a co-solvent to aid solubility. In the USA, maximum permitted quantities in over the counter (OTC) products: <0.5% for children under 6-years, <5% for children 6-12-years, <10% for children over 12-years. The effects of ethanol on the paediatric population have only been elucidated in the cases of acute and chronic poisoning. These effects include: hypoglycaemia, acidosis, loss of consciousness, hypothermia and tachycardia. Long term effects on hepatic and neurological function have been documented. There is paucity of information on the physiological effects of ethanol in paediatrics apart from poisoning (7).

Benzyl alcohol is used as a common preservative in many injectable drugs. Together with its derivative benzoic acid, benzyl alcohol has been associated in the past with toxicity and death in neonates who received injectable flush or lavage saline solutions containing benzyl alcohol. Neonates, especially if ill, may not be able to adequately metabolize benzyl alcohol [8]. High concentrations can lead to breathing difficulties, vasodilation, low blood pressure, seizures, and paralysis.

Propylene glycol is commonly used in topical, oral and injectable formulations as a drug stabiliser. Neonates are vulnerable to its toxicity because they have a longer half-life (16.9 hours) compared to adults (5 hours). Adverse effects of its use include serum hyperosmolality, seizures at high doses of over 3g/day from intravenous solutions, central nervous system toxicity, cardiac arrhythmias, hemolysis and agitation [9]. The conversion of propylene glycol to lactic acid causes lactic acidosis. Other adverse effects include acute kidney injury, respiratory and central nervous system depression. Rapid infusion of propylene glycol containing medications causes respiratory depression, arrhythmias, hypotension and seizures [9].

Although most studies attribute adverse drug reactions to the active pharmaceutical ingredients, very few studies have studied the effects of excipients, particularly alcohol. A study in the UK neonatal intensive care unit demonstrated that neonates were exposed to an equivalent of 0.07 to 15.2 adult UK alcohol intakes per week, through excipients in medication [10]. There have been no studies in Kenyan patients and in pharmacies to demonstrate the content of potentially harmful alcohol excipients in paediatric medicines, which could contribute to adverse drug reactions reported in children. This study sought to shed light on the types and amount of alcohol in drugs dispensed to children in Nairobi.

Methods

A cross sectional study of selected community pharmacies in Nairobi was conducted between March and September 2015. Community pharmacies around Kenyatta National Hospital, which is the largest referral hospital in Kenya serving patients from all parts of the country, were selected. Patients who do not get prescribed drugs at the KNH paediatric pharmacy buy drugs at the pharmacies. From the list of selected 21 community pharmacies, every third pharmacy was selected, to form a sample of seven pharmacies.

The investigator sampled all paediatric drugs at all the selected pharmacies and perused the drug packages, labels and package inserts for information on alcohol content. Data on the name of the drug (brand and generic), type of drugs and their pharmacologic classification, type of alcohol, and alcohol content (percentage), was collected and entered into a pretested data collection form. Data was entered into a Microsoft Office Excel 2010 worksheet and descriptive data analysis done. The results were presented in form of charts and tables.
Results

1. Selected Pharmacies and Number of Paediatric drugs Sampled per Pharmacy

The study was carried out in seven community pharmacies around Kenyatta National Hospital whereby a total 290 drugs were sampled and out of the 290 drugs, 87 drugs were found to have alcohol. The pharmacies were coded with serial numbers for confidentiality. Pharmacy number 005 recorded the highest number of products with alcohol excipients (Table 1).

### Table 1. Number of drugs sampled at each pharmacy

<table>
<thead>
<tr>
<th>Community pharmacies</th>
<th>Total number of drugs sampled (n)</th>
<th>No of drugs with alcohol</th>
<th>Cumulative % from each sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>001</td>
<td>58</td>
<td>12 (13.8%)</td>
<td>20.7</td>
</tr>
<tr>
<td>002</td>
<td>55</td>
<td>13 (14.9%)</td>
<td>23.6</td>
</tr>
<tr>
<td>003</td>
<td>50</td>
<td>14 (16.1%)</td>
<td>28.0</td>
</tr>
<tr>
<td>004</td>
<td>45</td>
<td>13 (14.9%)</td>
<td>28.9</td>
</tr>
<tr>
<td>005</td>
<td>40</td>
<td>16 (18.4%)</td>
<td>40.0</td>
</tr>
<tr>
<td>006</td>
<td>30</td>
<td>13 (14.9%)</td>
<td>43.3</td>
</tr>
<tr>
<td>007</td>
<td>12</td>
<td>6 (6.9%)</td>
<td>50.0</td>
</tr>
<tr>
<td>Total</td>
<td>290</td>
<td>87 (100.0%)</td>
<td></td>
</tr>
</tbody>
</table>

2. Over the Counter Versus Prescription only Medication containing alcohol excipients

Most of the medication with alcohol comprised the OTC medication (79.3%) as opposed to 20.7% which were prescription only medication (Figure 1).

3. Pharmaceutical dosage forms and alcohol content

With regard to pharmaceutical dosage forms, syrups had the highest number of products with alcohol (58.6%) followed by solutions at 25.3% (Figure 2).

4. Pharmacological Class of Drugs and alcohol content

Antihistamines were the class of drugs with the highest number of products containing alcohol (39.1%), followed by cough suppressants (16.1%). The anti-epileptics had the lowest number of products with alcohol as an excipient (Figure 3).

5. Types of alcohol excipients

Ethanol was the most common type of alcohol excipient found in the drugs (46.0%, n=40), followed by propylene glycol (27.6%). Some product labels and inserts did not specify the type of alcohol contained in the drug but simply stated it as “alcohol” (25.3%, n=22). Benzyl alcohol was the least used excipient at 1.1% (Table 2).

### Table 2. Types of alcohol excipients

<table>
<thead>
<tr>
<th>Alcohol excipient</th>
<th>Frequency (n, %)</th>
<th>Cumulative % from sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>40 (46.0%)</td>
<td>13.8</td>
</tr>
</tbody>
</table>

Figure 1. Over the Counter and Prescription only medication with alcohol content

Figure 2. Pharmaceutical dosage forms with alcohol excipients

Figure 3. Pharmacologic class of drugs with alcohol excipients

Vol. 23, No 4 / Pharmaceutical Journal of Kenya / 2018
"Products did not specify the type of alcohol excipient but simply referred to them as 'alcohol'.

6. Product brand versus alcohol content

Out of the 87 products that contained alcohol, only 49 (56.3%) had the alcohol content specified. Of these, 55.1% (n=27) contained ethanol, while 44.9% (n=22) contained unspecified alcohol. The content of ethanol varied by product, and ranged from 0.1% to 9.6% while that of unspecified alcohol ranged from 3.6% to 5.0%. The alcohol content was not indicated for all products containing propylene glycol (Table 3).

Table 3: Product alcohol content by brand

<table>
<thead>
<tr>
<th>Product name</th>
<th>Active Pharmaceutical Ingredient</th>
<th>Frequency (n, %)</th>
<th>Alcohol content (% w/v)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchicum elixir</td>
<td>Herbal (Thymus vulgaris, Primula veris)</td>
<td>6 (15.0%)</td>
<td>4.9</td>
</tr>
<tr>
<td>Rhinathiol</td>
<td>Carbocisteine 250mg/5ml</td>
<td>7 (17.5%)</td>
<td>1.34</td>
</tr>
<tr>
<td>Ranferon-12 elixir</td>
<td>Folic acid, ferrous ammonium citrate, ferrous fumarate, cyanocobalamin, ascorbic acid, zinc sulfate</td>
<td>7(17.5%)</td>
<td>3.61</td>
</tr>
<tr>
<td>Tres orix forte</td>
<td></td>
<td>7(17.5%)</td>
<td>-</td>
</tr>
<tr>
<td>Flagyl</td>
<td>Metronidazole 200mg/5ml</td>
<td>6(15.0%)</td>
<td>-</td>
</tr>
<tr>
<td>Atarax</td>
<td>Hydroxyzine 10mg/5ml</td>
<td>3(7.5%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Ercefuryl</td>
<td>Nifuroxazide 218mg/5ml</td>
<td>4 (10.0%)</td>
<td>9.6</td>
</tr>
<tr>
<td>Benylin paediatric</td>
<td>Dextromethorphan HBr</td>
<td>7 (31.8%)</td>
<td>5</td>
</tr>
<tr>
<td>Piriton syrup</td>
<td>Chlorpheniramine maleate</td>
<td>7(31.8%)</td>
<td>3.6</td>
</tr>
<tr>
<td>Piriton expectorant</td>
<td>Chlorpheniramine maleate, ammonium chloride, sodium citrate</td>
<td>7(31.8%)</td>
<td>3.6</td>
</tr>
<tr>
<td>Plactinic</td>
<td>Cyprechtadine hydrochloride</td>
<td>1(4.5%)</td>
<td>5</td>
</tr>
<tr>
<td>Claritin</td>
<td>Loratadine</td>
<td>6 (26.1%)</td>
<td>-</td>
</tr>
<tr>
<td>Aerius</td>
<td>Desloratadine 0.5mg/ml</td>
<td>6(26.1%)</td>
<td>-</td>
</tr>
<tr>
<td>Zyrtec</td>
<td>Cetirizine HCl</td>
<td>6(26.1%)</td>
<td>-</td>
</tr>
<tr>
<td>Tegretol</td>
<td>Carbamazepine</td>
<td>2 (8.7%)</td>
<td>-</td>
</tr>
</tbody>
</table>

7. Alcohol consumption per daily dose of drug

For the drugs whose alcohol content was indicated, we calculated the equivalent daily dose of alcohol intake through excipients by children, using the daily dosing regimen for each drug. Ercefuryl had the highest alcohol content per dose per day, followed by Plactinic. The European Medicines Agency recommends that the amount of alcohol excipient should be stated in terms of its equivalent amount of beer or wine, using 5% alcohol content for beer and 12% for wine. Using this, we calculated the equivalent amount of alcohol in the medicines in terms of volume of beer consumed per day (Table 4).

Table 4: Equivalent amount of alcohol in medicines

<table>
<thead>
<tr>
<th>Drug</th>
<th>Active ingredient</th>
<th>Maximum daily dose</th>
<th>% alcohol content (w/v)</th>
<th>Daily alcohol dose (mg)</th>
<th>Equivalent amount of beer/day (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bronchicum elixir</td>
<td>Herbal (Thymus vulgaris, Primula veris)</td>
<td>15ml</td>
<td>4.9</td>
<td>735</td>
<td>14.7</td>
</tr>
<tr>
<td>Rhinathiol</td>
<td>Carbocisteine 250mg/5ml</td>
<td>15ml</td>
<td>1.34</td>
<td>201</td>
<td>4.02</td>
</tr>
<tr>
<td>Ranferon-12 elixir</td>
<td>Folic acid, ferrous ammonium citrate, ferrous fumarate, cyanocobalamin, ascorbic acid, zinc sulfate</td>
<td>10ml</td>
<td>3.61</td>
<td>361</td>
<td>7.22</td>
</tr>
<tr>
<td>Atarax</td>
<td>Hydroxyzine 10mg/5ml</td>
<td></td>
<td>0.1</td>
<td>25</td>
<td>0.5</td>
</tr>
<tr>
<td>Ercefuryl</td>
<td>Nifuroxazide 218mg/5ml</td>
<td>15ml</td>
<td>9.6</td>
<td>1440</td>
<td>28.8</td>
</tr>
<tr>
<td>Benylin paediatric</td>
<td>Dextromethorphan HBr</td>
<td>10ml</td>
<td>5</td>
<td>500</td>
<td>10.0</td>
</tr>
<tr>
<td>Piriton syrup</td>
<td>Chlorpheniramine maleate</td>
<td>15ml</td>
<td>3.6</td>
<td>540</td>
<td>10.8</td>
</tr>
<tr>
<td>Piriton expectorant</td>
<td>Chlorpheniramine maleate, ammonium chloride, sodium citrate</td>
<td>15ml</td>
<td>3.6</td>
<td>540</td>
<td>10.8</td>
</tr>
<tr>
<td>Plactinic</td>
<td>Cyprechtadine hydrochloride</td>
<td>15ml</td>
<td>5</td>
<td>750</td>
<td>15.0</td>
</tr>
</tbody>
</table>

8. Recommendations for paediatric use by age

Different drugs had different recommendations for children less than 6 years and those more than six years old as shown in Figures 5 and 6. Only 3 drugs containing ethanol as an excipient were recommended for use in patients below 6 years of age. A total count of 24 and 22 drugs which contained ethanol and alcohol respectively were not recommended for patients below 6 years of age. All products containing propylene glycol did not have labels for recommended use in children less than or more than six
years old. There were variations in recommendation of use by product in children older than six years old.

Figure 5: Number of drugs recommended for children below 6 years

A total count of 8 and 23 drugs containing alcohol and ethanol respectively were recommended for patients above 6 years of age. A total count of 4 and 14 drugs containing ethanol and alcohol respectively were not recommended for patients above 6 years of age. There were no recommendations for both groups for drugs containing propylene glycol and benzyl alcohol.

9. Recommendation of use of drugs across pharmaceutical dosage forms

Recommendations for use of products varied across the different pharmaceutical dosage forms as illustrated in Figures 7 and 8. For drugs containing ethanol, syrups were the most commonly recommended for use in children below six years of age. There was no recommendation for drugs containing the unspecified alcohol and propylene glycol. For those above six years, syrups were the most recommended for use for products with ethanol and unspecified alcohol.

Figure 7: Recommendation for patients below 6 years

Figure 8: Recommendation for patients above 6 years

Discussion

In our study, over the counter (OTC) products were found to have more products containing alcohol (79.3%) compared to prescription only drugs (21.7%). This can be explained by the fact that there is tighter regulation for prescription only medication compared to over the counter medication. Antihistamines comprised the highest number of products with alcohol as an excipient in our study, and most of them are OTCs. Additionally, most OTCs include vitamin preparations, herbal and homeopathic preparations, which require a significant amount of alcohol in their formulation [3].

Syrups had the highest percentage of alcohol as an excipient (68.6%) compared to solutions, followed by suspensions. During formulation of drugs, several factors are considered when selecting the appropriate excipient. The pH at which the drug is most stable should be close enough to the solubility of the drug required to deliver the drug in approximately 5ml. Oral solutions and syrups are therefore developed in this case. Suspensions are formulated when the pH of the drug is not close enough to the solubility. This explains the fact that syrups and solutions, as opposed to suspensions had the highest number of products with alcohol [11].
Even though the package inserts of drugs like Atarax (hydroxyzine), Piriton (Chlorpheniramine), Ercufuryl (nifuroxazide), Benylin (dextromethorphan), Flagyl (Metronidazole) and Rhinathiol (Carbocisteine) indicated that alcohol should not be taken with these drugs, they still contained alcohol excipients. Alcohol can potentiate drowsiness caused by the antihistamines such as hydroxyzine, chlorpheniramine as well as cough medicines like dextromethorphan. Hydroxyzine is one of the drugs used to treat alcoholism, and has been shown to interact with alcohol. Metronidazole, when taken together with alcohol, causes disulfiram like reactions, which present with vomiting, tachycardia, flushing, visual disturbances, hypotension, syncope and circulatory collapse [1].

Ethanol and propylene glycol were the most commonly used excipients in our study. This agrees with studies that show that it is the most commonly used excipient after water [7]. Even though ethanol use in medicines has been discouraged due to interaction with other drugs, diseases, effects on performance and driving, pregnancy and breastfeeding, it continues to be widely used as an excipient [3].

In children, metabolism of alcohol varies with age due to immature systems. The effects of ethanol in children have been reported in acute intoxication and they include: hypothermia, hypoglycaemia, coma, seizures, hypotonia, hyporeflexia, gastritis, acute hepatitis and pancreatitis, hypokalemia and lactic acidosis. A study demonstrated these effects in paediatric intensive care patients [10]. The use of ethanol in medicines has been restricted in Europe, but there has been no such restriction in Kenya and other developing countries [3].

Propylene glycol is a potentially toxic excipient. It can cause life threatening effects like seizures, lactic acidosis, hyperosmolality, acute kidney injury and respiratory and central nervous system depression [9]. In our study, its content was not specified in the drug packaging and inserts. Omission of information and inaccuracy in labelling of drugs may expose children to these adverse reactions, especially if the content of excipient is high [6-8].

For the drugs whose alcohol content was specified, the alcohol content ranged from 0.1% to 9.6%. The World Health Organisation (WHO) proposes that the amount of ethanol in OTC preparations should be less than 0.5% for children less than 6 years old, less than 5% for children 6-12 years old and less than 10% for children over 12 years. In our study, most of the products with the stated alcohol content were not recommended for use in children less than six years of age.

The French Medicines Agency recommends that if ethanol is included in medicines for children, the amount of ethanol contained should not produce a blood alcohol concentration of more than 0.125g/l. The total volume of alcohol in the medication should be such that it should not exceed 3g/kg in case the entire bottle is consumed by a child. The FDA recommends that in case alcohol is included as an excipient, the blood alcohol levels should not exceed 0.25g/dl, and all over the counter liquid products, including topical products, should not contain more than 5% ethanol. In our study, some products had higher than the recommended 5% alcohol level content. This can be explained by the fact that there are no regulations from the Pharmacy and Poisons Board on labelling for the alcohol content and recommended blood alcohol level for paediatric products in Kenya.

The European medicines Agency recommends that package inserts of drugs containing ethanol should state its equivalent volume in terms of beer and wine, with 5% ethanol used for beer and 12% for wine. In our study, the daily consumption of alcohol for the drug with the highest amount of alcohol was equivalent to 28.8 ml of beer. This was not indicated on the packaging as there are no Kenyan guidelines for that.

There were several limitations to our study. First, a lot of the paediatric medications selected, especially the generics did not indicate the presence of excipients in their packaging. Only branded drugs did. Of the drugs that indicated the presence of alcohol, only few of them indicated the alcohol content. We were not able to verify the content of alcohol in the drugs through laboratory testing due to time and financial constraints.

Conclusion

Over the counter drugs had more products containing alcohol than the prescription only drugs. Ethanol and propylene glycol were the most commonly used alcohol excipients. The propylene glycol content was not stated in all products containing it. The highest amount of alcohol per daily dose of drugs was equivalent to 28.8 ml of beer. Most of the products were not recommended for children less than 6 years old.

Conflict of Interest

We declare that we have no conflict of interest.

References


24. MacDonald MG,Getson PR,Miller MK .Propylene glycol:increased incidence of seizures in low bith weight infants. Paediatrics 79


Abstract
Glucose-6-phosphate dehydrogenase deficiency (G6PDd) is an X-linked hereditary genetic defect that is estimated to affect 400 million people worldwide. This deficiency is associated with hemolytic disorders that may manifest depending on the molecular variant present, exposure to hemolytic triggers such as consumption of foods including fava beans and exposure to drugs including dapsone and primaquine. This disorder has been found to be more prevalent in malaria endemic zones of Asia, Africa and South America. This study determined the occurrence of G6PD deficiency among the donors at the Regional Blood Transfusion Centre-Mombasa, and whether any correlation existed between the occurrence of G6PD deficiency and either ABO blood type or haemoglobin concentration.

Methaemoglobin reduction test was used to check for the presence of G6PDd among the blood donors, anti A and anti B sera were used to determine the blood types. Haemoglobin concentration was estimated using haematology analyzer. Multivariate analysis was done to establish the point prevalence of G6PDd in the donor population, the relationship between G6PD and ABO blood types and the correlation between G6PDd and haemoglobin concentration. Out of the 676 donors 9.6% were deficient of G6PD activity while 13.17% had red cells exhibiting partial activity. The point prevalence for all forms of G6PDd was found to be 22.79%. Blood group AB donors were least likely to exhibit G6PD deficiency compared to the rest of the ABO blood types.

Key Words: Transfusion, Glucose-6-Phosphate dehydrogenase, deficiency, blood donors.

Introduction
Red blood cells are an important part of the body’s metabolic processes. With a lifespan of 120 days, the non-nucleated red cells perform their metabolic functions and are also able to perform their specialized core function of oxygen transport and delivery to the body tissues [1].

The transfer of oxygen across cell membranes and its utilization are dependent on the cytochrome P24 group of molecules, the Embden Meyerhof glycolysis pathway and the hexose monophosphate shunt. The free oxygen radicals that are produced during these processes are harmful to cells and tissues [2]. To mitigate the effects of these free radicals, various enzymes and metabolic intermediates are involved in these glycolytic pathways. These include the 2-3 diphosphoglycerate, pyruvate kinase and glucose 6 phosphate dehydrogenase (G6PD) enzymes [3]. Glucose-6-phosphate dehydrogenase plays an important role in all cells particularly the red blood cells (RBC) [4]. It protects the cells from potential damage by reactive oxygen species (ROS) [5]. G6PD reduces nicotinamide adenine dinucleotide phosphate (NADP) to nicotinamide adenosine dinucleotide phosphate hydrogenase (NADPH). The NADPH then reduces oxidised glutathione (GSSG) to reduced glutathione (GSH). The reduced glutathione is then able to bind to the ROS and protect the cells from oxidative stress [6]. The lack of mitochondria in the RBCs make the action of G6PD vital in the protection against oxidants [5]. A Glucose 6 Phosphate Dehydrogenase deficiency (G6PDd) would therefore be potentially hazardous to Red Blood Cells (RBCs) in particular due to their role in oxygen...
transport. The G6PDd was first reported by the Greek philosopher Pythagoras who noticed that the consumption of fava beans resulted in an ailment to some of his subjects, which he named favism [4].

The G6PD gene has been shown to have several mutant alleles that have decreased enzyme activity thus expressing the G6PD deficient phenotype [7]. The deficiency of G6PD enzyme is an X-linked recessive in-born error of metabolism [2]. This condition predisposes individuals especially males to acute red blood cell haemolysis and neonatal jaundice. The condition occurs in the presence of exogenous factors such as consumption of fava beans, oxidative stress due to infections, anaemia and certain drugs among them dapsone, methylthioninium chloride (methylene blue), nitrofurantoin, phenazopyridine, primaquine, rasburicase and tolonium chloride (toluidine blue) [8]. G6PDd is the most common genetically determined red blood cell enzyme deficiency in the world [1]. Currently about 160 different variants of G6PDd have been isolated and it is estimated that 400 million people are affected worldwide [1]. The disease presentation in most individuals is largely asymptomatic in the absence of exogenous triggers [9]. In severe variants however, G6PD deficiency may result in non-spherocytic haemolytic anaemia even without oxidative stress [10]. The manifestations of severe haemolysis due to G6PDd start early and has been implicated as a common cause of severe neonatal jaundice [11]. Enzyme deficiencies have been implicated in hemolytic symptoms after transfusion and are viewed as potentially fatal to patients transfused with such blood [12,13]. The reaction of nitrites with haemoglobin may be exploited to screen donors for G6PD. Sodium nitrite converts the haemoglobin to haemiglobin via an autocatalytic reaction that involves the formation of methaemoglobin and nitrate as the stable end product [14]. The current study aimed to determine the occurrence of G6PD deficiency amongst blood donors at the Regional Blood Transfusion Centre – Mombasa and the correlation between occurrence of deficiency and ABO blood type or haemoglobin concentration.

Methods

This was a cross-sectional study conducted in Mombasa Kenya. Samples were collected from donors at the Regional Blood Transfusion Centre (RBTC) Mombasa and analysis done at the Technical University of Mombasa department of medical science laboratories. Ethical review was obtained from the Pwani University Ethical review board under reference number ERC/MSc/009/2017. A no objection statement was also obtained from the Director, Kenya National Blood Transfusion Service.

A total of 676 samples were drawn from donors recruited and bled by the RBTC staff. These blood samples were assayed for G6PD activity using the Methaemoglobin reduction method. One milliliter of blood was added to a 0.1mL combined nitrite, dextrose and methylene blue reagent and the two mixed by inversion. Methylene blue was then added to stimulate the pentose phosphate pathway. Control tubes comprising of one milliliter of blood without reagents and another containing sodium nitrite without methylene blue were also mixed. All the tubes were then incubated at 37°C for 90 minutes. 0.1mL of the mixtures were then obtained and subjected to lysis using 10mL of distilled water.

The presence of various degrees of lysis was representative of the G6PD activity of the sample. Normal blood takes the color of the normal reference tube (clear red), G6PD deficient blood takes the color of the deficient reference tube (brown). Intermediate reactions will show the presence of heterozygote G6PD conditions. ABO blood type was assayed using microtiter plates and reagents ACCUCARE™ (Lab-care diagnostics, India) blood type using the anti “A” and anti “B” sera these were used to correlate with the findings of the G6PDd to check for association. Haemoglobin concentration was estimated using the Medonic TM haematology analyzer. Consent was inferred after the donors signed the donor health assessment questionnaire. All information obtained was treated with confidentiality in conformity to the Kenya National Blood Transfusion Service (KNBTS) guidelines on donor records. Prior permission to use the samples was obtained from the director of KNBTS. The study was approved by the Pwani University Ethical Review Board (PU-ERB).

Results

Overall G6PD deficiency

A total of 676 samples were assayed for G6PDd. Donor samples showing complete deficiency in G6PD activity were 9.6% of the total donors assayed. Intermediate reactions were observed in 13.2% samples. The total number of donors having G6PDd was 154 (22.8%) of the donor population. The proportion of normal and abnormal blood samples based on G6PD enzyme activity was 77.2% and 22.8%, respectively (fig. 1).

![Figure 1: Proportions of G6PD activity in the blood samples collected at the Regional Blood Transfusion Centre (RBTC) Mombasa, Kenya.](Image)
Correlation between ABO blood type and G6PD occurrence

Figure 2. Correlation between the ABO blood types and the occurrence of glucos 6 phosphate dehydrogenase deficiency in the donor population

The test results showed that there was a marginal correlation in the likelihood of having G6PDd between blood type AB and type A. Blood type A individuals had a higher likelihood of having G6PD deficiency compared to blood type AB individuals. The Chi square test for association showed that there was a correlation between ABO blood type and occurrence of G6PD deficiency (p-value 0.003989) A marginal significance of AB in reference to Blood type A was observed. Donors with Blood type AB were more likely to be normal compared to those of Blood type A (coef=1.09, s.e =0.63. p-value=0.08).

G6PD in relation to Haemoglobin concentration

Table 1: relationship between haemoglobin and G6PD condition in donors

<table>
<thead>
<tr>
<th></th>
<th>HB&lt;12.0</th>
<th>HB&gt;=12.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>10.5%</td>
<td>89.5%</td>
</tr>
<tr>
<td>INTERMEDIATE</td>
<td>7.9%</td>
<td>92.1%</td>
</tr>
<tr>
<td>DEFICIENT</td>
<td>10.8%</td>
<td>89.2%</td>
</tr>
<tr>
<td>ABNORMAL</td>
<td>9.1%</td>
<td>90.9%</td>
</tr>
</tbody>
</table>

Analysis of variance (ANOVA) showed that at least one of the G6PD groups had a different Haemoglobin concentration than the others with a calculated F-value of 0.0426 (CI 95%) this was not however reflected in the pairwise comparisons.

Discussion

The current study shows a point prevalence of 9.6% for homozygous G6PD and 13.2% showing heterozygosity. A point prevalence of 22.8% for all forms of G6PD was found amongst the donors assayed (figure 1). Studies worldwide have shown that the G6PD deficiency offers either partial or full resistance to P. falciparum infection and has therefore been found in polymorphic proportions in malaria endemic areas [15]. These studies show that the condition is predominant in Asia and sub-Saharan Africa [4]. A study in Yemen found that among healthy male donors, 7.2% had G6PDd in the capital city of Sanaa. In Kenya, the estimated prevalence for G6PDd is in the range of 10% to 13% [15]. The current study compares favourably with the results from Nigeria by Akanni et al., who found a prevalence of 19.5% in blood donors in Osogbo, [16] and Nguetse et al., who reported that 73% of the study subjects in selected African countries had normal G6PD activity [17]. However these findings do not correspond with estimates by Howes et al which indicate that prevalence of G6PDd in Kenya is about 13% [15]. This may be due to the high prevalence rate of malaria in the coastal region. G6PDd has been shown to have a high prevalence in malaria endemic zones [15]. The association of G6PDd with health conditions is a major area of study today. Akanni et al have associated neonatal jaundice to the deficiency showing 47% of the jaundiced neonates in the study were G6PD deficient [16]. It has also been found that altered G6PD activity may play a critical role in severe pulmonary hypertension [18]. This study established that G6PD condition of a donor was associated with ABO blood types (figure 2). A marginal significance was established between the A and AB Donors. A person with Blood type “A” was more likely to be deficient than a person with blood type “AB” at a p-value 0.03989 (coefficient of variance=1.09, Standard error=0.63. p-value=0.08). The relationship between G6PD deficiency and haemoglobin concentration was difficult to establish (Table 1) even though an ANOVA model revealed that there is indeed a difference between the G6PD condition and the Hb levels of the donor (F-value 0.0426, CI 95%). This correlation is not however reflected in the pair wise comparisons. Future studies to incorporate a larger sample size needs to be done to establish this relationship.

Conclusion

Glucose 6 phosphate dehydrogenase deficiency is present in donated blood at the regional blood transfusion center, Mombasa. ABO type “A” individuals seem to have a marginally higher probability of having G6PD deficiency in comparison to the “AB” blood type. The percentage occurrence of G6PD is higher than has been previously estimated. There is therefore need to determine the presence of this condition in donors for documentation and reference, and in neonates when jaundice of unknown origin is encountered. The effect of G6PD deficient blood to the recipients is still a grey area that should be investigated further. There was a marginal statistically significant relationship between haemoglobin concentration of normal and G6PD deficient donors. This study was not however able to conclusively determine the relationship between G6PD and haemoglobin concentration. Further studies are needed to establish the relationship.

Conflicts of Interest

The authors declare no conflict of Interest.
Acknowledgements

Special thanks to The Technical University of Mombasa for providing an enabling environment space and funding support for the project.

We are grateful to The Kenya National Blood Transfusion Service director and The Regional blood transfusion center – Mombasa staffers who enabled us to collect samples during their blood campaigns.

References

Abstract

Background: Devolution of health services in Kenya was intended to enhance access to health care services. It is not clear to what extent this has been achieved.

Objective: To establish the perspectives of health care managers on the impact of devolution on health systems within Homa Bay County.

Methodology: We performed a health facility based qualitative study, adopting a phenomenological approach. The study population comprised all health care managers in eight public health facilities in Homa Bay County. The study used quota sampling involving different cadres of health care providers. Seven informants were interviewed in each sub-county leading to a total of 56 informants. Data was collected by use of structured interview guides and analyzed by a thematic approach.

Results: Progress of devolution was reported to be experiencing several challenges. The factors that were cited as bottlenecks to achieving full benefits of devolution were poor medical supplies, poor human resource recruitment and retention practices, remuneration uncertainties, corruption, nepotism and political interference. The main positive outcome of devolution was cited as enhanced community participation in health care issues. Opinion was divided as to whether devolution of health care should stay or be reversed.

Conclusions: From the foregoing, it is evident that devolution of health care is yet to be embraced fully by health care managers. Further studies to enhance evidence informed decision making is necessary.

Keywords: Devolution, health care, provider perspectives, Homa-Bay County.

Introduction

Since the year 2013 when the health docket was devolved in Kenya, resistance to devolution of health care services by health care providers has been a consistent theme in discussions with stakeholders in the sector. Perceived or real, there are fears that the devolved governments are not capable of handling the daunting task of providing universal access to healthcare services in the country. Initially, the resistance was seen in practising health care providers, but empirical research has now documented similar sentiments even from trainee health care workers in our local Universities [1]. Because of devolution, they have lost interest in working in the public health sector in the country and look forward to working in the private sector upon graduating. The public health managers in the county governments have in the recent past complained about the work environment, transition challenges, restricted decision space, resource constrains and uncertainty among other challenges in rolling out devolution of health care services [2]. They also complained of poor work conditions like inadequate housing, water supply, electricity supply, and educational facilities [3]. From a study in Pakistan, the typical bottle necks for progress of devolution include lack of a clear devolution policy, poor coordination among different sectors of the economy, restricted decision space, resource constrains and uncertainty among other challenges in rolling out devolution of health care services [4]. A similar study in Kilifi County, Kenya, also found out that the process of implementation of devolution presented opportunities for local level prioritization and community involvement in health planning. However, these opportunities were not adequately harnessed due to poor preparation and lack of capacity building by the devolved units prior to the implementation [5]. Implementation problems are also cited as impediment to devolution from a study in Tanzania [6]. In this study, they decreed sub-optimal multisectoral collaboration, low community participation and inappropriate and weak information systems as some of the specific impeding factors. On the other hand, the main gain aimed at when devolving health care services in different countries is to improve access to and public participation in health and health care decision making at the grassroot level. It is therefore probably proper to postulate that as much as the health care providers may be complaining, the citizens may be very optimistic about devolution despite the challenges
experienced so far. This is evident from the findings of a study on the impact of devolution on health planning and administration in Cote D’Ivoire [7, 8]. Some studies have shown that devolution has shown signs of likelihood of equity and edging towards universal health coverage in Kenya and other Countries [9,10]. This is not only because it removes transportation barriers to care [11], but also because it improves ownership and public participation by citizens in their health care decisions thus leading to better quality and socially acceptable health decisions [12,13]. There are scholars who argue that benefits of devolution would accrue mostly to regions with full fiscal and political power and which were rich before devolution [14]. If this is true, then Homa-Bay County, which has been one of the poorest in the country, may take long before experiencing the benefits of devolution. People in such far-flung areas, emerging from previously centralized and nearly authoritarian health decision making culture, are likely to be ignorant of the benefits of devolution [15,16]. Targeted health and civic education may therefore help them realize the full utility of devolution of health care services especially with respect to making use of the new decision space through community participation. For meaningful benefit of devolution to be realised, the interests of the user communities, political elites and health care providers must be taken care of [17]. The objective of the study was to establish the perspectives of health care managers on the impact of devolution on health systems within Homa Bay County.

Methods

Study design: The study was conducted as a health facility based qualitative study, adopting a phenomenologi-c approach. The reason for using qualitative research approach in this study was to illicit in-depth views of health care managers on the impact of devolving health care services in Homa Bay County

Study Population: The study population comprised all health care managers in public health facilities in Homa Bay County. The County has one referral hospital in Homa Bay town and seven sub County hospitals. In each of these facilities, there is a Sub-County Medical officer of Health, Medical Officer in Charge, Pharmacist in Charge, Nursing officer in charge, Health administrator, a public health officer in charge and the head of the medical laboratory department. These form the health management team and were therefore purposively selected as the key informants for the study.

Sampling Procedure and sample size. The study used purposive sampling to settle on the health managers to interview as key informants. A total of 56 key informants were interviewed from the eight sub-Counties, with each sub-County having seven informants. Saturation of data was anticipated after 12 to 15 interviews [18, 19]. Theoretical saturation of data was experienced after 25 interviews, but we continued with the interview for completion purposes until we interviewed all the 48 respondents.

Data collection procedure: Data was collected by use of structured interview guides. The interview guides were pre-tested in Migori County and further refined as the study progressed.

Data Analysis: Data was analyzed by a thematic approach. The key themes used in the analysis were financing, infrastructure, human resources, pharmaceutical supplies, community participation, overall process of implementing devolution and whether it should be reverted to the national government or not.

Ethical Considerations: Research authorisation was obtained from the Kenyatta National Hospital/University of Nairobi-Ethics and Research Committee (Ref- P389/05/2016). Voluntary informed consent of the participants was also obtained before recruitment into the study. Participants were informed about the study purpose, procedures, benefits, risks and their rights as participants. The participants were free to leave study at any time without any consequences to them. They were however not compensated or paid to participate in the study. Confidentiality was ensured by use of codes to represent participants instead of their names. Data was kept safely in a computer under a password available to the principle investigator only.

Results

The baseline socio-demographic characteristics of the respondents were as summarized in the table 1 below.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Attribute</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Below 30 years</td>
<td>7</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>31 to 50 years</td>
<td>22</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Above 50 years</td>
<td>19</td>
<td>44</td>
</tr>
<tr>
<td>Designation</td>
<td>Medical Officer I/C</td>
<td>8</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>Pharmacist I/C</td>
<td>8</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>Nursing Officer I/C</td>
<td>8</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>Lab Tech I/C</td>
<td>8</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>Matron</td>
<td>8</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>Hospital Admin</td>
<td>8</td>
<td>16.7</td>
</tr>
<tr>
<td>Highest Level of education</td>
<td>Post-Graduate Degree</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td>Tertiary</td>
<td>9</td>
<td>19</td>
</tr>
<tr>
<td>Number of years in service</td>
<td>Below 5</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>5-20</td>
<td>22</td>
<td>46</td>
</tr>
<tr>
<td></td>
<td>Above 20</td>
<td>19</td>
<td>39</td>
</tr>
</tbody>
</table>

The interviews revolved around one stem question with sub-questions. The stem question was, ‘In your opinion, how has devolution of health care services impacted on the following issues in Homa-Bay County?

1. Pharmaceutical supplies including procurement procedures and policies

On the pharmaceutical commodities supplies procedures
and policies, most of the respondents gave reasons why devolution has made matters worse as follows;

On professionalism being applied especially in tendering for the medical supplies, most of the respondents faulted the County government. For example, a pharmacist in one of the referral hospitals had this to say.

‘Things are not being done professionally. Today, drugs are procured even without the knowledge of the pharmacist in charge. There are more stock outs. Suppliers are chosen based on cronynism. It is not structured. There are many unethical practices. Because of corruption, technical staff is not involved, and drugs don’t reach health facilities’- Informant Number 1, Hospital Number 1.

Political interference from the county government and county assembly was cited as the main reason for the lack of professionalism in the procurement procedures. They were viewed as non-professional outsiders of the medical professions but who wield greater power delegated to them by the people compared to the health care providers.

‘Things have become worse because the challenge is that people at the top are not professionals. Tenders are given to those are friends or relatives. Some top management people have never worked on the ground. They are also hired politically’ Informant Number 4, Hospital Number 8.

Another issue that came up prominently was lack of prompt payment of the Kenya Medical Supplies Authority (KEMSA) thus delaying supply of medicines and other supplies. This was seen to derail the restocking of medicines hence denting the confidence of health are users on the health systems of the county.

‘OK. What I can say, mmh....... when we were receiving drugs from the national government, KEMSA used to supply antimalarials regularly. Now, we don’t get even the antimalarials from KEMSA. Commodities are now difficult to procure. KEMSA doesn’t supply because of late payment. We understand that since last year, KEMSA has never been paid. We therefore have problems with pharmaceutical and other supplies. Pharmaceutical supplies have become inconsistent. Like now, the last time we got drugs was March. Again, quantities are also small. It appears KEMSA people are not sure about transition of counties’- Informant Number 3, Hospital Number 6.

On the other hand, a respondent thought that devolution has helped to improve procurement procedures as captured in the statement below.

‘Mmh......it’s OK because the counties do their orders from KEMSA directly. We haven’t had so many negative issues. We are not experiencing any problem with procurement. They have been supplying us well. We are supplied quarterly. Earlier, we had pull and pull system. Today, what you order is what you are given’- Informant Number 2, Hospital Number 3.

2. Health care financing including donor funding and budgetary allocation

Most of the informants reported that devolution had worsened health care financing in the County. Despite most of them agreeing that donor funding has been the pillar of funding for most programs, they also stated that County governments were responsible for making the funding to stagnate. The words of the respondent quoted below paints a picture of despair and desperation on matters of funding of health programs in the County after the onset of devolution;

‘Generally, funding is poor for all departments in health. You can plan as a team, yet disbursement is not there. When it comes, it comes too little too late. The situation is worsening. The county is not releasing money to facilities. All the funds end at the County. Quarterly remissions are no longer there. Since devolution started, I don’t know whether County government has scared donors. They no longer pump a lot of money especially on health programs. We rely 75 % on facility improvement fund, not county government’- Informant Number 1, Hospital Number 2.

It also became apparent that most free maternity money is often diverted to other health care issues when the County government does not allocate or release enough money for health care services. For example, a respondent in one of the sub-county hospitals said;

‘Particularly, what we receive regularly is free maternity money. The rest is erratic and hence unreliable. The county government also slashes even the free maternity money. It is true that the donors are funding the trainings of health care workers on malaria case management. However, the county government does not allocate funds for malaria. We survive on our collections and free maternity money’

Informant Number 3, Hospital Number 7.

In the Contrary, an informant stated that financing of health programs improved with devolution. They however acknowledged that the improvement could be attributed mainly to the efforts of the development partners and not often the County government per se.

‘Financing is better under devolution. Like recently we had a malaria prevention campaign funded by a donor organization. So far, the funding is good. PSI supplies us with nets consistently. We have partners supporting malaria programs. The county government and NGOs support malaria programs especially in pregnancy and under-fives’ Informant Number 2 Hospital Number 6.

3. Cost of health care borne by the patient

On whether patients now pay less or more for services after devolution of health care services, majority of the informants felt there was no major difference before and after devolution.

‘Generally speaking, there is no change in cost borne by the patients. We still charge the same prices for services and drugs and cost sharing is still the same. Waiver forms are also available. But now, the problem is that they must buy almost everything else apart from laboratory diagnosis and medicines’
Respondent Number 3, Hospital Number 8.

Others believed that since the advent of devolution, patients pay less compared to before devolution.

‘Patients bear less costs. The county government is very close to the people. They know malaria is a major problem here. It is almost free. They may pay only 20 shillings for registration. It is like now the common citizens have a say on their health. Since devolution, in this facility, staffing has improved, services are of better quality and patients wait less’ Respondent Number 2, Hospital Number 4.

The role of NHIF was hailed as very important in helping the patients to bear less cost.

‘I don’t know but because nowadays we have NHIF cover for patients and most people use them, those who have them pay less but those who don’t pay much more. I don’t think devolution has helped a lot like the NHIF cover. Since devolution, uptake of NHIF by the patients has increased and release of money by the fund has also improved. You can see even now I am working on some payments which are due’ Respondent Number 1, Hospital Number 1.

4. Healthcare infrastructure and equipment

Majority of the informants felt that the County government had done nothing or too little to improve healthcare infrastructure and equipment in the county.

‘The county government is totally not helpful. We do not have a lot of equipment we need. We have forwarded requisitions to county government to buy or repair. Before devolution, there was money for such repairs and maintenance. Totally it’s poor today. For example, there is a building where the national government was to provide three quarters (¾) of the cost and the county government a quarter (¼). It is not complete to date and there are no equipment’ Informant Number 4, Hospital Number 4.

Some informants stated that the situation of infrastructure has improved with devolution

‘Devolution has brought a lot of development in so far as infrastructure is concerned. In our facility for example, we have a new renal unit, theatre, ultrasound, x-ray and oxygen plant. All these I can associate with devolution as much as it is the national government that provided most of them. We now have modern first-class machines. They are just like what you would find in Aga-Khan or Nairobi Hospital. This was not possible before devolution’ Informant Number 2, Hospital Number 1.

Maternity was cited as the greatest focus of health infrastructure development in the county since the advent of devolution. This may be because of the financial support from the national government since the inception of the National free maternity program.

‘Maternity wing has been constructed and this now has created demand for maternity services unlike before devolution when this facility was a health center. The good thing is that with devolution, many facilities have been elevated thus forcing the county government to provide infrastructure to match the new status’ Informant Number 2, Hospital Number 5.

‘There is a lot of improvement. Maternity is being built. The equipment are ready waiting but am not sure whether the equipment came from the county government or from the national government. The building am sure is being constructed by the county government’ Informant Number 1, Hospital Number 3.

Others also attributed improvement in infrastructure to support from partners rather than the county government.

‘There are no labs and no RDTs especially in the dispensaries. The county government has not done a lot of improvement. All equipment here are supplied by partners like UNICEF and MSF’ Informant Number 1, Hospital Number 4.

5. Community involvement in health matters

On whether the community is now more involved in health decisions after devolution compared to before, the respondents largely agreed that devolution has made it easier for the community to participate in their health matters. This was mainly attributed to the community strategy which revived the role of community health workers(CHWs).

‘Good. They have upgraded and employed new community health workers and community health officers. They have also created awareness and demand for healthcare services. Community strategy is working. Community health volunteers a lot of rapid diagnostic tests but this is sponsored mainly by the donor partners. Devolution has led to recruitment of more community health workers on the ground. Community dialogue is good, but the impact is not yet very good because the girl child education is still poor. However, in general, it is better because we have community strategy where the community health workers have direct involvement with the community. They give essential drugs and gather health data from the community’ Informant Number 2, Hospital Number 5.

Other respondents also attributed the improvement to the role of local politics through the members of county assembly (MCAs). This is most likely because they are now more recognized by law, better remunerated and bear a greater expectation of accountability to the people. Their sentiments were generally captured by the following respondent.

‘It is better. They think they own the county government. In case of anything, they know whom to complain to because the government is now closer to the people. There is a local person who is the chairman of the hospital. They are involved. If they are not satisfied, they give him feedback. MCAs are also involved as they get feedback from the people’ Informant Number 4, Hospital Number 6.

One respondent, however, felt that devolution has indeed
worsened community involvement in health matters. She said that;

‘There are a lot of problems. Even ward administrators should oversee the process of involving the community, but they don’t know their role and they have no resources for that. The community is involved minimally since devolution started’ Informant Number 2, Hospital Number 7.

6. Recruitment and retention of health workforce

Majority of the informants felt that staff welfare became worse with devolution. They had varied reasons as captured below;

**Corruption and nepotism;**

‘Recruitment is not being done professionally. People employ who they know. Retention is not good. No promotions and payment of salaries delays. For example, today is 15th and Doctors haven’t received their salary for last month. People rarely get leave. Study leave applications are not processed. There are no structures here’ Informant Number 1, Hospital Number 8.

**Late payment of monthly salaries;**

‘There are no enough laboratory personnel. It has not improved. The county is not employing people. Motivation is not very good. There is a lot of movement to the private sector. Even today, we have not been paid last month’s salary, yet it is already mid-month’ Informant Number 2, Hospital Number 6.

**Employment is not based on need on the ground.**

‘What I can say is, what the county is doing is not recruiting clinical staff. People we are getting from the county are support staff. For example, all in patient nurses are employed by MSF. Promotion has become an issue. Maybe they fear spending’ Informant Number 2, Hospital Number 4.

A few respondents felt that recruitment and retention of health workforce had improved with devolution. However, all of them had some aspect of dissatisfaction appended to their approval.

‘We have received a good number of officers but not optimum. They have better retention strategies except for delays in salaries which makes people anxious. What I can say, if you compare with the number which was there before, there is improvement. We are receiving staff. We only don’t know the criteria for their appointment. Even partners are recruiting for the County’ Informant Number 3, Hospital Number 3.

7. The general quality of health care services in the County

Most of the informants felt that devolution had a negative impact on the quality of health care services in the county. They gave the following as some of the reasons for the deterioration.

**Lack of adequate staffing;**

‘Generally, how can we gauge this. Well, compared to national government, the county government has not done well as was expected. We don’t have professionals. They bring equipment, but buildings are not complete. X-rays and computers are not repaired. Sometimes we go manual and no one addresses the Devolution is failing. Informant Number 2, Hospital Number 6.

**Incompetent management and political interference;**

‘Eh!........for me as an individual who worked in the national government, I would prefer the national government. The quality of care has gone down. Everything has become political. With the counties, they have brought health closer to the community. But, a lot still needs to be done. They don’t employ enough clinicians. Nepotism is rampant, and accountability is little. Today, many pharmacists and pharma techs are leaving public service because of late and poor payment and bad work environment. All this is due to political interference’ Informant Number 4, Hospital Number 5.

**Inadequate funding;**

‘The only thing they are doing is employment, but drugs and money are not there. Here is a small place so collections are not enough. In a year, they may give us money once and it may not be enough. There is a time I was talking to a nurse and she said there are delays in disbursal of free delivery funds. The free delivery is therefore not really free since they have to buy a lot of things. The county government should improve on the process of approving finances’ Informant Number 2, Hospital Number 4.

Those who thought devolution had improved the quality of health care services in Homa-Bay county supported their feelings with the following points;

**Community strategy improving employment of community health workers;**

‘There is an improvement. The improvement is seen at the preventive and promotive level. Those in community malaria management strategy give RDTs and if they don’t have they refer. Health care has generally improved except for delays’ Informant Number 1, Hospital Number 5.

**Better staffing;**

‘It has improved because new health care providers have been employed. There are so many health care providers who have been employed since devolution came in’ Informant Number 4, Hospital Number 3.

**Proximity of health services to the people;**

‘It is in a way better because in the past, Nairobi was far. Today, all clients have direct access to the county government in one way or another. In case of any problem, they intervene fast’ Informant Number 3, Hospital Number 2.
8. Should health docket remain devolved or returned to the national government

On this matter, most of the respondents strongly felt that health care should be reverted to the national government. One of them expressed her opinion as captured below;

‘The interest of health care providers is that health care should go back to the national government. I think the political leadership should consider this. We don’t have much to do in the County government. Devolution of health care was more of an error. We don’t see these current problems being solved soon. County governments don’t even want to employ doctors. Even if you come, they keep you away. I think for me one thing is seconding staff to counties was done in a hurry and it's inappropriate. The government should find a way of financing facilities directly without money going to the county treasury’ Informant Number 1, Hospital Number 8.

There are a few informants who felt that devolution is a good idea and only needs to be reinforced. The had following is a typical example of their views.

‘What I think is, devolution was a good idea poorly implemented especially on health. It is not performing as expected. However, going back to national government will not help. I think they should just work on the weak areas and strengthen it’ Informant Number 3, Hospital Number 1.

Discussion

The feelings of health care managers concerning the impact of devolution on health systems were mixed. However, majority of the informants seemed to agree that there are so many challenges that if left unchecked, could reverse the little gains achieved so far by devolution. Such challenges were cited as nepotism and cronynism, lack of proper recruitment procedures, political interference in the professional work of health care providers, waste of resources, late payment of salaries and poor supply chain management among others. Devolving healthcare was intended at taking services closer to the people. They would then have more say on the quality and access to healthcare services offered to them [7]. To date, this objective seems not to have been adequately realized since challenges such as inadequate medical supplies, and low staff morale persist even after devolution much like they were before [3]. These challenges were attributed to corruption, nepotism, poor financial management and political interference by the members of County assembly on the work of clinicians. These results concur with those of a study in Kilifi County that found that management of health care services in the era of devolution was marred with lack of job clarity and preparedness, unclear accountability and responsibility structures coupled with shortages in key resources and remuneration inconsistencies. [2]. Similar findings were also reported from a study in Pakistan [20]. However, healthcare, by its very nature, is highly political. Many politicians are interested in the politics of health care which they use as a platform to propagate their own political agenda. This is because they know that almost all citizens hold health care very dearly. This is a reality that needs to be internalized by county health care managers and service providers if they are to survive in the murky waters of health care and politics [21]. Funding of health programs by development partners seems to have slowed down after devolution. Another problem cited by most informants was that money meant for free maternity care was often diverted to other uses in times of scarcity. These findings show that health policies need to work in support of each other and not eat into the gains of one another. For example, if the proponents of free maternity services could have foreseen a situation where the funds meant for free maternity services could be diverted to other medical services, they could have advocated for better funding for all other essential health care services and not only the maternal health component. Health infrastructure development was reported to be lagging and the main reason given for this trend was that health budget was often redirected to other sectors. Recruitment and retention of health workforce was also said to be poor. The respondents stated that the County government employed so many support staff and few clinical service providers thus ballooning the wage bill with no significant improvement in direct health service delivery. The main positive impact of devolution seems to be community involvement in health care decisions. Most informants mentioned that since the implementation of devolution, most citizens got more interested in health care governance since they gained a sense of ownership. The County government also deliberately strengthened the community strategy policy to increase public participation in health policy debates. These finding contrast those of a study in Tanzania which observed that despite national rhetoric on decentralization, the actual practice in the field had little community involvement [22]. This poor participation was attributed to lack of awareness, poor communication and information sharing unclear definition of roles and responsibilities, lack of management capacity and lack of financial resources [23]. Opinion on whether health docket should be returned to the national government was divided as some thought this was overdue, yet others felt that devolution was actually a good idea poorly and hurriedly implemented and if the mistakes of implementation are corrected, there would be no need for reverting health care to the National government. As it has been observed in other developing countries, the progress of devolution of health care is often slow but with desirable outcomes in the long run [24]. A little patience and persistence would therefore be necessary to push our health devolution agenda to fruition.

Conclusions

From the findings of this study, it is evident that devolution of health care is yet to be embraced fully by health care managers. There seems, however, to be goodwill since most of the managers seemed positive that devolution can work if the bottlenecks are addressed. Health managers need to
adapt to policy and political shifts following devolution to effectively manage health services in the era of devolution. The County government also needs to address the gaps in implementation of devolution such as late salaries, poor medical supplies and improper recruitment procedures.

References


Guidelines for Contributors

AIMS AND SCOPE OF THE PHARMACEUTICAL JOURNAL OF KENYA

The Pharmaceutical Journal of Kenya (PJK) is devoted to publishing original research manuscripts, reviews, letters to the Editor, and short communications. The PJK covers all aspects of medicines, health and life sciences. PJK provides a platform to all practitioners, researchers, academicians, students, and industrialists to share their ideas, knowledge, information and research findings among the people of their fraternity.

All submissions must be made in English.

EDITORIAL POLICY

The PJK accepts only original communications/manuscripts submitted exclusively to the journal. Prior and duplicate publications are not accepted. Publication of abstract under conference proceedings will not be considered as prior publication. It is the duty of the contributors to inform the PJK about all submissions and previous reports that might be considered prior or duplicates as publication will be considered on their individual merits after reviews.

PEER REVIEW PROCESS

All Submissions to the journal are initially reviewed and short-listed by the Editorial Board. At this stage manuscripts may be returned to the author for revision, before peer review, if the manuscript does not comply with Editorial policies. Thereafter, manuscripts are sent out for a double blind peer review (i.e. the reviewer will not know who the author is and vice-versa), usually to two independent reviewers.

After evaluation, the external reviewers shall choose between the following decisions:

1. Accept with minor revisions;
2. Propose major revisions that the authors must make, to address specific concerns before a final decision is reached; or
3. Reject, but indicate to the authors that further work might justify a resubmission.

If the decision is classified as ‘Minor Revision’ or ‘Major Revision,’ the author shall have 7 or 14 days, respectively, to resubmit the revised manuscript from the date of official communication of verdict.

Upon resubmission, and having been satisfied that such revision as may have been initially proposed has been made, the Editorial Board may choose to send them back to the reviewers, or may render a decision based on their expertise. The Editorial Board has the discretion of rejecting a manuscript whose author fails to revise upon such recommendation.

In special circumstances, the contributors may be asked to suggest referees working in the same area for evaluation, but the final choice of reviewers is a preserve of the Editorial Board.

ETHICS

The PJK highly values ethical practices in biomedical experiments. The ethical standards of experiments must meet the highest internationally accepted standards. Human and animal experimental procedures should have met ethical standards set by a competent Ethics and Research Committee. Evidence of approval by such a Committee must be supplied by the authors. The details of anesthetics and analgesics used should be clearly stated. The journal will not consider any paper which is ethically unacceptable. A statement on Ethics & Research Committee permission and ethical practices must therefore be included in all research manuscripts under the ‘Materials and Methods’ section.

It is mandatory that all research attributed to a manuscript must be carried out within an appropriate ethical framework. There shall be no infringement on human and animal rights. If a new technical advance has been used during research, the author must provide justification for employing such a non-conventional method.

ANTI-PLAGIARISM POLICY

Plagiarism is a criminal offense and punishable by law. PJK advises that all acceptable manuscripts must be solely the work of the authors, and in the event that ideas and/or works need to be borrowed, proper citation guidelines must be adhered to.
The PJK encourages authors to avoid the representation of words or ideas of others, wherefore the below guidelines must be observed at all times:

- Original content/work is highly recommended;
- When material is from any other source, the same should be paraphrased or summarized in whole or in part in one’s own words and must be cited properly according to Vancouver referencing style;
- Every direct quotation must be identified by quotation marks, with foot notes appropriately placed;
- When using other authors’ ideas as sources in writing a paper, the author shall bear the responsibility of representing those others’ ideas accurately.

The Editorial Board shall assess all papers for plagiarism prior to publication.

COPYRIGHT
Any manuscript published in the PJK will be the copyright of the Journal. The Journal will have the right to publish the accepted manuscripts in any media (print or electronic) any number of times.

CONFLICT OF INTEREST
A submission is accepted on the basis that there is no competing interest regarding the publication. Authors are required to disclose all potential conflicts of interest a priori. It is normal practice to acknowledge research sponsors and grantors when submitting manuscripts.

CO-AUTHOR CONSENT
Prior consent from co-authors of a manuscript must have been sought and agreement reached at the time of submission. The PJK Editorial Board shall not be held liable if such consent was not obtained.

FORMAT AND STYLE OF MANUSCRIPT
Authors should keep their manuscripts simple, explicit and as short as possible. Recent issues of the PJK should be consulted as a guide for the general format adopted in respect of various elements of a paper. Alternatively, authors are encouraged to contact the Editorial Board for any further clarifications. Identity of the author(s) must NOT appear anywhere in the manuscript, except on the first page.

SUBMISSION OF MANUSCRIPTS
Contributors should submit one electronic copy in MS Word as follows;

**Formatting of document Title**

- Font style: Times New Roman
- Font size: 12
- Lines: Not more than 2
- Abbreviations: None

**Formatting of document body:**

- Font style: Times New Roman
- Font size: 10
- Spacing: 1.5
- Page set up: 1 inch margin on all sides
- Pagination: Consecutively (page 1 of x)

**Presentation of Manuscripts**

a) Manuscript length: Not more than 12 pages
b) Authors: Lead author’s name first, surname followed by 2 initials e.g. Njuguna, A. K.
c) Authors’ affiliation (e.g. Institution), complete postal and email addresses.
d) Abstract: Not exceeding 300 words excluding the title and the key words. No abbreviations. Abstract not required for short communications or letters to the Editor. Presentation of Abstract to be similar to the format for content below (sub-titles ii – vi). The abstract must be concise, clear and informative.
e) Declaration of Conflict of Interest (if applicable)
f) Key words: 3-6 key words to be listed.
g) Declaration of sources of funding, technical or any other support related to the research/manuscript.

**Format for Content**

i. Abstract
ii. Introduction
iii. Aims/Objective/Hypotheses
iv. Methodology
v. Results
vi. Discussion/Conclusion and Recommendations
vii. References

**References – Vancouver Style**

References are to be cited using Vancouver style. Citations must appear in order of appearance in the text with square brackets after the end of a sentence, i.e., [3]. The citation must electronically refer to the Reference Listing at the end of the manuscript.

References cited only in tables or in legends to figures should be numbered in accordance with a sequence established by the first identification in the text of the particular table or illustration. Figures must be labelled at the bottom, whilst tables shall be labelled at the top.

The number of references should normally be restricted to a maximum of 25 for a full paper, whereby not more than 20% should be not more than 5 years old, and no more than 10% should be more than 10 years old. References older than 10 years should ideally be classical subject material references.

Papers which have been submitted and accepted, but not yet published may be included in the list of references with the name of the journal and indicated as “In press”. Use of abstracts as references should be avoided. The “unpublished observations” and “personal communications” may not be used as references but may be inserted (in parentheses) in the text.

**RIGHT TO REJECT MANUSCRIPT**

The editors reserve the right to reject a manuscript for publication if it does not meet the requirements of the Pharmaceutical Journal of Kenya.

**Manuscripts should be submitted to:**

The Editor-in-Chief,
Pharmaceutical Journal of Kenya,
P.O. Box 44290 – 00100 GPO,
NAIROBI, KENYA.
Email: pjk@psk.or.ke
Become A Member

In order to become a member with the Pharmaceutical Society of Kenya (PSK), you must provide your registration number. This information will be verified by the Secretariat before any member has access to their account.

Qualification

Member PSK (MPSK)

A graduate pharmacist registered by the Pharmacy and Poisons Board (PPB)

Fellow PSK (FPSK)

A full member who has rendered distinguished service to the society or in the field of pharmacy or who has made outstanding original contribution to the advancement of pharmaceutical knowledge or who has attained exceptional proficiency in a subject embraced by or related to the practice of pharmacy

PSK is a closed society. Membership is by annual subscription. Paid up members’ benefits include:

- Elect representation to elective and nominated positions
- Stand for elective and nominated positions
- Access to Professional networks both locally and internationally
- Publish on the Pharmaceutical Journal of Kenya (PJK)
- Access to members empowerment programmes