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FEATURE ARTICLE:

Accuracy of Splitting of Carbamazepine Tablets Available in the Kenyan Market

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CONTENTS

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

A revolution in Diabetes diagnosis and therapy

Editorial by Orwa JA, PhD.
Editor-in-Chief

The condition now known as diabetes has been documented since the dawn of time by scientists and physicians. In 1552 BC, Hesy-Ra, an Egyptian physician, documented frequent urination as a symptom of a mysterious disease. At the same time, Ancient Hindu writings noted that ants are attracted to the urine of people with a mysterious disease. The Egyptians recognized an ailment suspected to be diabetes approximately 1550 BC, and 500 BC saw the first descriptions of sugar in the urine and its occurrence in obese individuals.

Greek physician Apollonius of Memphis is credited with coining the term "diabetes," naming the disorder with its first symptom: the excessive passing of urine through the body's system in 250BC. Mellitus, the Latin word for honey, was added to the term diabetes. Physicians began to gain a better understanding about diabetes in 150AD and in 164AD Greek physician, Galen of Pergamum, diagnosed diabetes as a kidney ailment. Up to the 11th century, since the urine of people with diabetes was thought to be sweet tasting, diagnosis was often made by "water tasters" who drank the urine of those suspected of having diabetes. In 1953, tablets for testing urine glucose became widely available, and urine test strips appeared over the next few years.

In the early years of the 20th century, medical professionals took the first steps toward discovering a cause and treatment mode for diabetes. In 1923, Eli Lilly and Company began commercial production of insulin. In 1926, Edward Albert Sharpey-Schafer announced that the pancreas of a patient with diabetes was unable to produce what he termed "insulin," a chemical the body uses to break down sugar. Thus, excess sugar ended up in the urine. In the decades that followed, manufacturers developed a variety of slower-acting insulins, the first being Protamine insulin introduced by Novo Nordisk in 1936. In 1996, the drug Acarbose, brand name Precose (Bayer Corporation) became available in the U.S.A. Acarbose is an alpha-glucosidase inhibitor that slows digestion of some carbohydrates. Lispro (a lysine-proline analog) was introduced by Eli Lilly and Company as the world's fastest acting insulin.

Although insulin injection began to successfully combat diabetes, some cases were unresponsive to this form of treatment. Harold Himsworth finally distinguished between the two types of diabetes in 1936, according to writings published by his son Richard in Diabetic Medicine. He defined them as "insulin-sensitive" and "insulin-insensitive." Today, these classifications are commonly referred to as "type 1" and "type 2" diabetes.

In 1959 using radioimmunoassay technology, Solomon Berson, MD and Rosalyn Yalow, PhD developed a method for measuring insulin in the blood. They noticed that some people with diabetes produce their own insulin, and they identified "insulin-dependent" (type 1) and "non-insulin-dependent" (type 2) diabetes. In 1971 insulin receptors were discovered on cell membranes. This discovery raised the possibility that missing or defective insulin receptors may prevent glucose from entering the cells, thus contributing to the insulin resistance of type 2 diabetes.

In 1913 Allen's book - *Studies Concerning Glycosuria and Diabetes*, stimulated a revolution in diabetes therapy. Between 1910 and 1920, Allen and Joslin were considered the two leading diabetes specialists in the United States. Joslin believed that diabetes was "the best of the chronic diseases" because it was "clean, seldom unsightly, not contagious, often painless and susceptible to treatment." In 1916, Allen promoted a strict diet regimen, which was soon widely adopted. Allen believed that the diabetic's body could not use food, so he limited the amount of food allowed to patients. Patients were admitted to the hospital and given only whiskey mixed with black coffee (or clear soup for teetotalers) every two hours from 7am to 7pm. This diet was followed until there was no sign of sugar in the urine, usually 5 days or less. A strict diet followed. Outcomes were better than ever seen before for those with type 2 diabetes. Unfortunately, those patients with type 1 diabetes commonly died during the treatment, likely from starvation. A few young people did survive and became the first insulin users. In 1919, Allen published *Total Dietary Regulation in the Treatment of Diabetes*, with exhaustive case records and observations of 76 of his 100 diabetes patients.

The life expectancy for people with diabetes in 2004 was still lower than that for the general population by about 15 years. In 2014, 26 million Americans had diabetes and 1 in 3 of them was unaware. Another 79 million Americans were categorized as "pre-diabetic" and were at risk of developing diabetes in the next ten years if they failed to make appropriate lifestyle changes. Diabetes that was considered a disease of the affluent has now infiltrated the African region affecting the poor and wealthy in equal proportions. The World Health Organization (WHO) estimates that the prevalence of diabetes in Kenya is at 3.3% and predicts a

rise to 4.5% by 2025. However, two-thirds of diabetics may be undiagnosed. So is it a revolution or an evolution in diabetes therapy?

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Knowledge on Diabetes Mellitus and its Management Strategies among Diabetic Outpatients in a Tertiary Referral Hospital in Kenya

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Abstract

Background: Good knowledge about diabetes and its management enhances the ability of patients to cope and adjust to their illness.

Objectives: To determine the knowledge on diabetes mellitus and its management among diabetic outpatients at Kenyatta National Hospital, Diabetic Clinic.

Methodology: This was a cross-sectional study involving 105 consenting diabetic outpatients, aged ≥18 years. Consecutive sampling was used to collect data using pre-designed semi structured interviewer administered questionnaires. Patients' knowledge on diabetes mellitus including cause, symptoms, complications, medications, dietary control, importance of exercises and diabetes affiliate organizations was collected and analysed using IBM statistical package for social sciences version 21. Chi square tests were used to compute associations between participants' sociodemographics and outcome variables at p≤0.05.

Results: The ratio of males to females was approximately 1:1. The mean age of the participants and duration of diabetes was 41.0±16.0 and 6.0±5.0 years, respectively. Knowledge on causes, signs and symptoms of diabetes mellitus was statistically significantly associated with the education level (p=0.0001) and was more common among males (p=0.01). Knowledge on dietary control (p=0.02), exercise (p=0.04) and complications (p=0.05) was more common among males and the more educated. Irrespective of sociodemographic variables (p>0.05), only 33.3% of the patients knew their medication and dosing schedules in relation to meals. A large proportion (90%) of the patients was unaware of the role of diabetes affiliate organizations.

Conclusion: Knowledge on diabetes among diabetic outpatients varies with level of education and gender. More health education is, however, advocated to diabetic patients in order to increase their knowledge on antidiabetic medication and diabetes affiliate organizations. Future work should, however, be carried out to correlate the patients' level of knowledge and long term glycaemic control.

Keywords: *Diabetes mellitus, patient knowledge, control measures, antidiabetic medication, diabetic affiliate organizations.*

Introduction

Globally, diabetes mellitus (DM) is emerging as one of the

world's biggest healthcare problems and its prevalence is increasing at an alarming rate [1–3]. Many people are unaware that they have the disease [4–6]. Furthermore, some patients are diagnosed during routine check-ups on clinic visits as they do not know about the disease and DM complications may be the first presenting sign [7]. Owing to inadequate knowledge, some patients are treated for urinary tract diseases which mimic features of DM [8] while others are inadequately managed [9,10].

Studies have shown that patients' knowledge about the disease and control activities plays a vital role in its future development, early prevention, detection and optimal management as well as improved outcomes [11,12]. Most importantly, for chronic illnesses such as diabetes, emphasis is now placed on educational preventive programmes, early detection and control measures [11]. These strategies require the patient to be empowered through health education [13,14]. Nevertheless, available literature from some parts of Middle East has revealed that there is substantial poor knowledge on DM and its management among patients [15].

Treatment of diabetes involves both drug and non-drug methods (16). For instance, type I DM is treated with insulin, exercise, and a diabetic diet [17] while type II DM is initially managed with concurrent employment of a low glycaemic index diet and exercise before introduction of the medication [16,18]. The roles of exercise, controlled diet and medication are clear [18,19] and therefore, diabetic patients' knowledge on management measures is paramount for optimal blood sugar control [20]. Additionally, diabetes management activities require clear understanding of the disease manifestations and control strategies by the patient [21]. Furthermore, patients' knowledge on medications and lifestyle modifications can significantly reduce diabetes complications [20,22,23]. There is compelling evidence that good knowledge about DM and its complications enhances the ability of patients to cope and adjust to their illness whereas poor knowledge is associated with increased rate of hospitalization [24,25].

Patients with DM and their families provide more than 90% of the care [26,27] and as a consequence, knowledge on the disease and self-management are central components of any effective treatment plan (28). Additionally, patients with knowledge on diabetes and its management are more likely to participate in management and control activities [29,30] as knowledge is a critical component of behaviour change [31]. Moreover, patients' awareness of support groups or affiliate organizations such as diabetic associations is important for provision of knowledge and other essential management strategies [32].

This study, therefore, sought to measure the knowledge of diabetes, control measures and awareness of their organizations among diabetic outpatients at Kenyatta National Hospital with an objective of improving the practice of diabetes management.

Methods

Study approval (reference number KNH-ERC/01/4742) was obtained from Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee (KNH/UoN-ERC) and a cross sectional study was carried out in KNH diabetic clinic. The study population consisted of 105 diabetic patients aged ≥18 years who attended the clinic.

The study sample size was estimated using Cochran's formula [33]. There were no previous studies on the level of knowledge among diabetics attending KNH outpatient clinics. As such, it was estimated that the proportion of patients with adequate knowledge in each study variable would be 50% with an error margin of ± 10%. Using these proportions at 95% confidence level, the minimum sample size was calculated as 96 participants. However, to allow for data losses and non-responders, a 10% was added to the estimated sample size to make total of 105 DM respondents.

Participants were eligible if they were aged ≥18 years, had been diagnosed with DM and were on treatment. Both males and females were invited to participate in a face to face interview. Pregnant and lactating mothers were excluded as their treatment modalities could have been altered by their status. Only eligible DM patients who gave written, signed, informed consent to participate were interviewed consecutively by the researcher as they came for clinic appointments.

Semi structured serialized questionnaires were used to collect the raw data. Every questionnaire was assigned a unique alphanumerical serial study number to avoid confusion and duplication of the data. Patients' identifiers such as names or their file numbers were not recorded. The questionnaires were designed to capture participants' sociodemographic characteristics such as gender, highest education level and age as well as clinical characteristics including duration of diabetes, treatment modalities and respondents' knowledge and importance on each of the management strategies. Participants were evaluated on their understanding of the disease pertaining to the causes, signs and symptoms of DM.

Respondents' knowledge on the possible complications of diabetes and the organs affected were also assessed as well as on their medication pertaining to the name of the drug they were using, the time of the day they were required to take in relation to meals and the dose. Those who were using insulin therapy were required to tell the type and units that they were injecting at different times of the day in relation to meals. Final knowledge assessment was conducted on participants' awareness of the role of diabetes affiliate organizations. The answers given by patients were written in the questionnaire as accurately as possible. The information collected was kept confidential at all times.

Each measurable parameter had a series of questions to be answered by the patient. Questions were rated at a 100 per

cent for each parameter. Therefore, for every parameter, the patients' level of knowledge was expressed as a percentage by taking the number of questions correctly answered by the patient divided by total number of questions in each parameter, and the answer multiplied by 100.

Since, there were no previous studies on the level of knowledge among diabetic patients, a participant who scored 50% and above in each of the measurable parameters was termed to have sufficient knowledge in that particular parameter. A patient who scored less than 50% was termed to have insufficient knowledge in the respective parameter.

The raw data were keyed into Microsoft Access 2010 computer database structure resembling the questionnaire. When data entry was completed, it was cleaned by checking the data entered into the computer database against questionnaires. Any errors identified during data clean-up were rectified. The data were then exported to IBM statistical software version 18 for analysis. Descriptive statistics on frequencies of the participants' sociodemographics characteristics were done. Chi square tests were used to compute the associations between the participants' socio-demographic data versus the outcome variables such the level of knowledge on the disease, dietary control, exercise, complications, antidiabetic medication and diabetes affiliate organizations. The level of confidence was set at 95% and all values with $p \leq 0.05$ were considered statistically significant. Tables and graphs were presented for important findings.

Results

Out of a total of 105 diabetic adult outpatients who participated in the study, there were 53 (50.5%) males and 52 (49.5%) females. The mean age was 41.0±16.0 years and mean duration of diabetes was 6.0±5.0 years. There was an almost even distribution of participants across all the age categories and >60% of the patients had reached at least secondary level of education (Table 1).

Table 1. Socio-demographic characteristics of the study participants (N=105)

Variable	Category	Frequency (N=105	Percent (%)
Age Category (Years)	18-30 31-40 41-50 51-60 61-70 Above 70	12 24 21 21 22 5	11.4 22.9 20.0 20.0 21.0 4.8
Age Years Duration of illness (years)	(Mean, SD) (Mean, SD)	**(41.0, 16.0)** **(6.0, 5.0)**	
Sex	Male Female	53 52	50.5 49.5
Highest Education level	Non-formal Primary Secondary College/University	11 25 42 27	10.5 23.8 40.0 25.7

Key: SD-Standard deviation

Figure 1 below shows the proportion of patients and the level of knowledge across the study variables.

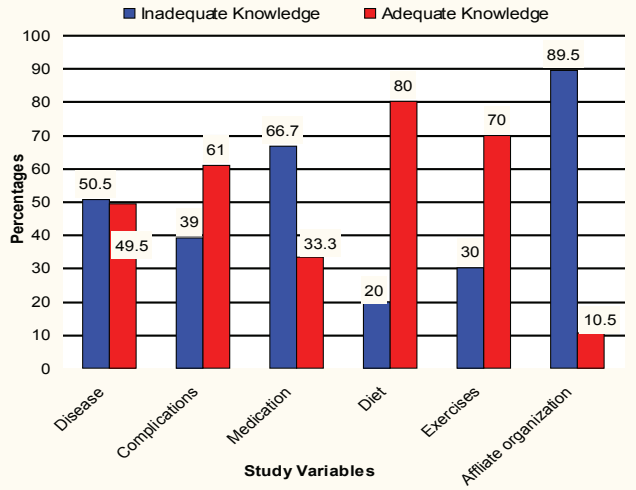

Figure 1. Proportions of patients with adequate knowledge on the various study variables.

Key: Disease-Knowledge on causes and manifestations of DM

As seen in Figure 1, more than half of the patients had sufficient knowledge on dietary control (80%) and the role of exercise (70%) in managing diabetes as well as on complications (61%). Conversely, there was inadequate knowledge on the diabetic medication and the role of DM affiliate organizations in more than two-thirds of the participants. Knowledge about the disease and its clinical features was evident in almost half (49.5%) of the patients interviewed (Figure 1).

The study also explored the adequacy of patients' knowledge on the disease and, the role of dietary measures and medication in the management of diabetes across the age categories as well as education levels. This was noted in order to find out the patients' age bracket or education level that would require emphasis regarding education on disease, medication and dietary measures because the three are paramount in management of diabetes. The findings are shown in figures 2 and 3 below.

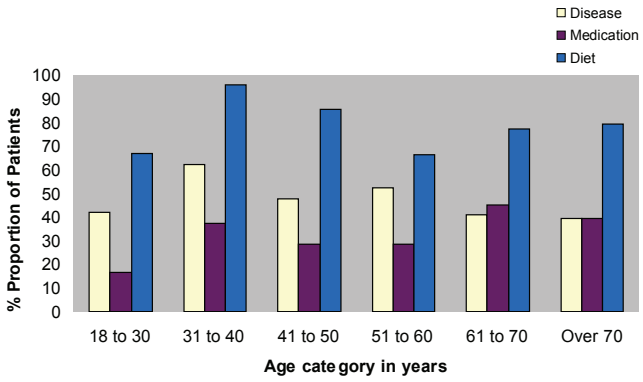

Figure 2. Proportions of patients with adequate knowledge on disease, medication and diet according to age.

Key: Disease-Knowledge on causes and manifestations of DM

Almost 40-50% of the patients in studied age categories had adequate knowledge about the DM and its clinical manifestations. Over 60% of the respondents in all the age categories had adequate knowledge on the importance of dietary control in the management of DM. Knowledge on antidiabetic medication was insufficient in over 60% of patients across the age categories and was worse at 18-30 years age bracket where less than a fifth (16%) of the participants had adequate knowledge (Figure 2).

Knowledge on disease, dietary control measures and medication was also evaluated against the highest academic level of the study participants.

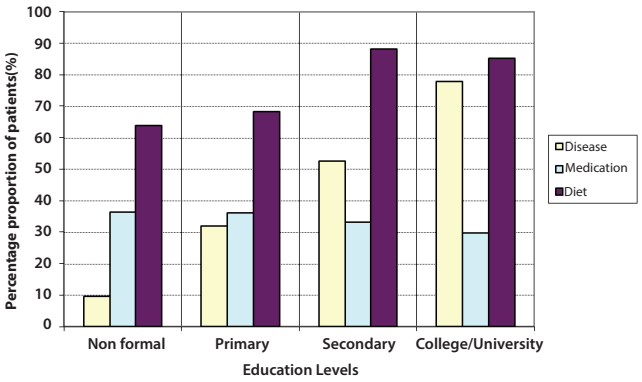

Figure 3. Proportions of patients with adequate knowledge on disease, medication and diet according to education level.

More than 60% of the respondents at all education levels had adequate knowledge on the importance of dietary control in the management of diabetes mellitus. However, less than 40% of the patients across the ages did not have adequate knowledge on antidiabetic medications. The proportions of patients with adequate knowledge about the disease increased with the level of education (Figure 3). This was statistically significant (p=0.0001) as seen in table 3 below.

Tables 2 and 3 below reveal the bivariate analysis for associations between the predictor and outcome variables. Adequacy of knowledge on the various study variables (outcome) was assessed against the predictor variables including gender of the participants (Table 2) and other sociodemographics such as age and highest education level (Table 3).

Table 2. Association between adequacies of knowledge on the measured variables by gender.

Adequacy of Knowledge		Males, n (%)	Females, n (%)	Chi square, P-value
Disease	Yes	30 (28.6)	2(20.9)	$X^2_{(1,5.05)}$=21.46 (p=0.01)
	No	23(21.9)	30(28.6)	
Diabetes Medication	Yes	17(16.2)	18(17.1)	$X^2_{(1,5.05)}$=3.097 (p=0.08)
	No	36(34.3)	34(32.4)	
Dietary Control	Yes	45(42.8)	19(18.1)	$X^2_{(1,5.05)}$=16.10 (p=0.02)
	No	8(7.6)	33(31.4)	
Diabetes Complications	Yes	34(32.4)	30(28.6)	$X^2_{(1,5.05)}$=4.60, (p=0.05)
	No	19(18.1)	22(20.9)	
Exercise	Yes	39(37.1)	34(32.3)	$X^2_{(1,5.05)}$=8.333 (p=0.04)
	No	14(13.3)	18(17.1)	
Affiliate organizations	Yes	4(3.8)	7(6.7)	$X^2_{(1,5.05)}$ 0.979, (p=0.32)
	No	49(46.7)	45(42.9)	

The proportion of males with adequate knowledge on the diabetes and its manifestations (p=0.01), diet (p=0.02), complications (p=0.05) and exercise (p=0.04) was statistically significantly higher than that of females. However, there was no gender disparity on the proportions of patients with adequate knowledge on antidiabetic medication and the awareness of affiliate organizations in the management of diabetes (Table 2).

Table 3. Associations between the measurable outcome variables with the participants' demographics of age and highest academic qualifications

Predictor variables	Outcome Variables					
	Disease	**Complication M**	**edication**	**Diet E**	**xercise**	**Affiliate organizations**
Age category	$\chi^2_{(5,0.05)} = 2.847$ (p=0.72)	$\chi^2_{(5,0.05)} = 60.750^*$ **(p=0.03)**	$\chi^2_{(5,0.05)} = 3.671$ (p=0.60)	$\chi^2_{(5,0.05)} = 7.958$ (p=0.16)	$\chi^2_{(5,0.05)} =$ 28.810* (p=0.07)	$\chi^2_{(5,0.05)} = 45.030^*$ **(p=0.05)**
Highest Education levels	$\chi^2_{(3,0.05)} = 19.024^*$ **(p=0.0001)**	$\chi^2_{(3,0.05)} = 0.999$ (p=0.19)	$\chi^2_{(3,0.05)} = 0.292$ (p=0.96)	$\chi^2_{(3,0.05)} = 62.650^*$ **(p=0.01)**	$\chi^2_{(3,0.05)} = 34.530^*$ **(p=0.03)**	$\chi^2_{(3,0.05)} = 4.386$ (p=0.22)

statistically significant

Adequate knowledge on diabetes complications (p=0.03) and importance of diabetes affiliate organizations (p=0.05) were statistically significantly associated with patients age. On the other hand, knowledge on disease presentation (p=0.0001), dietary control in the management of diabetes (p=0.01) and importance of exercises for a diabetic patient (p=0.003) were statistically significantly associated with the participants highest academic level.

Discussion

This study sought to find out the patients' knowledge on diabetes and various aspects of disease management. It revealed that only 49.5 % of diabetic patients could identify the cause and clinical manifestations of diabetes which is comparable to similar findings in Pakistan(15). In the Pakistanian study which involved knowledge and risk assessment, only 47.4% of the participants could identify the cause of diabetes. This proportion is, however, low considering that patients' awareness of their medical condition promotes optimal disease management (34). The small proportion suggests most of the diagnosing clinicians do not explain to patients the causes and manifestations of diabetes despite the fact that inadequate knowledge on disease impacts on its management and adherence to medication (14,35).

Eighty per cent of the patients interviewed had adequate knowledge on importance of dietary control. This is comparable to other studies that found 63.1% of the

participants with adequate knowledge on dietary control (15). The small difference could be attributed to the difference in the current study smaller sample size (105 vs. 198) and the fact that the latter study examined knowledge of oil use in cooking among diabetics (15). Studies have revealed that education on dietary control among DM patients is conducted by physicians, nurses and dietician immediately following diagnosis (25,36). Probably majority of the respondents had gone through education on dietary control measures following the diagnosis of diabetes mellitus, thus explaining the large proportion of patients with adequate knowledge on the parameter.

We observed that DM patients were advised to split the menu into about six small meals per day, rather than the traditional three square meals to prevent dangerous post prandial hyperglycaemia as has been revealed in other studies (16,35,37). Studies have also reported that diabetic patients are required to eat low glycaemic index foods that do not turn into sugar quickly (37). They are advised to eat fewer calories in order to maintain ideal body weight and refrain from taking excessive proteins (35).

Adequate knowledge on diabetes complications and exercise were exhibited by 61% and 70% of the participants, respectively. Similar studies have shown 60.6% of the participants with adequate knowledge on the exercise but a smaller proportion of 19.1% knowledge on complications (15).The conflicting figures are probably due to the fact that the latter study looked at adequacy of knowledge of diabetes complications in non-diabetic patients.

One-third (33.3%) of patients had adequate knowledge on use of antidiabetic drugs and was worse at 18-30 years age category (16%), which probably comprised of newly diagnosed individuals with minimal experience in managing the disease. Related studies have revealed that diabetic patients' education on rational use of antidiabetic medicines is important for maintenance of adequate glycaemic control in diabetes (25,35). It was observed that regardless of age, sex and the education level, patients did not know the dosing of the drugs in relation to meals.

It was also found that most insulin users did not know appropriate injecting techniques, the appropriate sites of injection and storage requirements for the drug (38). Majority of the patients were unfamiliar with the units (IU) of insulin but were more conversant with the millilitres (ml) of measurements. The likely explanation to this observation was that healthcare providers might have not adequately instructed patients on proper usage of their antidiabetic drugs, which is important in diabetes management. Additionally, it was likely that the healthcare providers did their best, but lack of an expert counselling in drug use at the diabetic clinic was encountered. There is considerable evidence that counselling on medication by an expert in drug use enhances the patient's understanding and adherence to medication (39,40).

Adequate knowledge on majority of study variables was found to be better in males than females. For instance, compared to females, there was a statistically significant proportion of males with adequate knowledge on disease (p=0.01), dietary control (p=0.02), complications (p=0.05) and exercise (p=0.04). Similar studies on knowledge on diabetes have found that male sex was statistically significantly associated with adequate knowledge (15).The reasons as to why there was sex disparity in knowledge level and yet DM has no gender predilection requires further investigation. On the other hand, although diabetes affiliate organizations are vital in supporting DM patients in managing the disease (32), only 10.5% of our respondents were aware of their existence and role. There was no gender or education level predilection on adequacy of knowledge on diabetes organizations although statistically, the elderly patients showed to have better awareness (p=0.05) than others but the number (n=5) was too small to draw meaningful conclusions.

Most of the patients who had attained university and secondary education had adequate knowledge about diabetes mellitus (p=0.0001), diet (p=0.01) and exercise (p=0.03) compared to those with primary and non-formal education. A similar finding where higher education level has been positively correlated with adequate knowledge on diabetic management measures has been revealed in similar studies (15). A possible reason for these findings could be that the highly educated patients are better placed in understanding the importance of dietary control and doing exercises in the management of DM. There is also a possibility that the highly educated patients read more about diabetes mellitus and its management in other references like textbooks, magazines or internet because they are assumed to have a better understanding.

The main limitation for this study was that we did not know how frequent the interviewed patients came for diabetes training in the hospital. Secondly, as common with cross-sectional studies involving interviews, patients could have over-reported or under-reported their experiences.

Conclusions and Recommendations

Knowledge on causes and clinical features of diabetes mellitus, use of antidiabetic medication and the importance of diabetes affiliate organizations is poor among diabetic outpatients attending KNH. Health education should be emphasized so as to increase awareness and knowledge on rational use of antidiabetic medications, especially among the younger population. Health education among DM patients should be tailored to their highest education level and gender. Lastly, future work should, however, be carried to correlate the patients' level of knowledge and long term glycaemic control. It may also be necessary to do qualitative study or larger samples over long period of time to clarify why males did better in knowledge level than females in the majority of variables studied.

Conflict of Interest Declaration

The authors declare no conflict of interest.

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Patterns and Predictors of medication use practices during pregnancy at the Kenyatta National Hospital, Nairobi, Kenya

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Abstract

Background: The study set out to establish drug use practices among mothers and prescribers at the Obstetrics and Gynaecology department of Kenyatta National Hospital. Since it is difficult to determine effects on the foetus before marketing new drugs due to ethical reasons, most drugs are contraindicated in pregnancy. However, pregnancy itself often necessitates medication. A careful balance between the risks of medications to the foetus and the benefits to the mother is therefore necessary. The study assessed patterns and predictors of drug use practices in pregnancy among women admitted to the labour wards of Kenyatta National Hospital. It was carried out as a cross sectional survey at the Obstetrics and Gynaecology wards of Kenyatta National Hospital. Data was analysed using STATA 13 computer software. Knowledge on medication use was measured by a score generated by combining ten variables of knowledge. Association between predictors and knowledge was done by chi square and logistic regression. Up to 70% of the respondents had practiced self-medication with at least one drug during pregnancy.

Paracetamol was the most used for self-medication (30%) while antibiotics were the most prescribed. FDA category B drugs were most prescribed (43.6%). Univariable analysis showed significant relationship between level of knowledge and age greater than 35 years, employment whether in the formal or informal sector compared to not being employed or self-employed and level of education. However, in the multivariable analysis which adjusted for other factors, only level of education was significant for having knowledge of drug use in pregnancy. These results provide sufficient evidence to conclude that level of knowledge of a mother on drug use in pregnancy significantly influences her self-medication practices while pregnant. This implies that a lot of effort should be put towards improving level of education of women as this will improve their reproductive health outcomes.

Keywords: *Medication use, Self-medication, Prescription, Pregnancy.*

Introduction

Drug use in pregnancy is rampant despite recommendations discouraging the same (1). Absolute avoidance of drugs in pregnancy is not realistic. However, their judicious use is more practical (2). Birth defects are observed among 3.5% to 5% of infants examined at birth or during neonatal period (3). As many as 1% of congenital abnormalities are caused by drugs, chemicals and other exogenous agents. However, the magnitude of the problem of medication use during pregnancy may be worse because 65-70% of birth defects have unknown aetiology (4). Pregnancy complications due to drugs and chemicals exposure are potentially preventable. Knowledge of the effects of pre-natal exposure and the opportunity for intervention are most important in reducing the complications (5).

Due to lack of evidence on safety, most drugs are not recommended to be used during pregnancy (6). For this reason, there are gaps in the knowledge about their teratogenicity. Drug use by pregnant women should therefore be viewed as a public health issue (7). The dilemma is that while avoidance of most drugs is recommended, especially in the first trimester (8), pregnancy itself is often a cause of need for drug use (6). For example, Indomethacin is commonly prescribed in pregnancy for the treatment of pain or as a tocolytic agent. Its use in pregnancy may cause oligohydramnios, premature closure of foetal ductus arteriosus with subsequent persistent pulmonary hypertension of the new born, foetal nephrotoxicity and periventricular haemorrhage (9). A careful balance between the risks of medications to the foetus and the benefits to the mother is therefore necessary (10).

Objective

The objective of the study was to establish the predictors of self-medication and prescription drug use during pregnancy at Kenyatta National Hospital, Kenya.

Methods

Study design

The study was conducted as a cross sectional survey. Only consenting conscious and clinically stable patients present in the wards at time of the survey were recruited to participate in the survey.

Study Population

Data on knowledge and practices on medication use in pregnancy was collected by the investigator over a period of four weeks on a population of mothers who were admitted to the Obstetrics and Gynaecology wards for delivery during the period of the study. Information regarding the use of prescribed drugs by the respondents was obtained from their medical records.

Study Sample

The minimum sample size (n) required for determining the prevalence of unsafe drug use in pregnancy was calculated using the Fisher's formula.

$$n=Z^2pq/e^2$$

Where

n=desired sample size

Z=standard normal deviate which 1.96 at 95% confidence level

P=percentage of women estimated to be practising self-medication during pregnancy

q=(1-p)

e=level of error allowed

Therefore, n = $(1.96)^2$x 0.2 x 0.8/ $(0.05)^2$= 245.86 (246). A total of 250 respondents were sampled for the study.

Only women who were present at the obstetric wards at the time of data collection having been admitted for purposes of delivery were included in the study. Those who were unable to communicate effectively due to labour pains or other medical complications during pregnancy were excluded from the study.

Sampling Procedure

A simple random sample of mothers who were present in the wards was taken by tossing a coin for every mother who fitted the inclusion criteria.

Data Analysis

To develop a model for analyzing the relationship between various respondent characteristics and knowledge on appropriate medication use during pregnancy, a knowledge score was generated by combining ten knowledge variables into a single variables; how they knew their pregnancy status, knowledge of danger of drugs to the foetus, effects of drugs on foetus, the trimester when drugs can have greatest effects on the foetus, whether counselled or not on drug use in pregnancy, if they used

self-medication drugs during pregnancy, effects of tobacco and alcohol on the foetus, specific drugs likely to affect pregnancy, source of information on drug use in pregnancy and knowledge of malformed organs. All variables included for generating the score contributed equally to the score. An individual's knowledge was then reported as a score out of ten. Knowledge was then grouped using the mean knowledge score (6.7) to generate a binary variable as having or not having knowledge. The new knowledge score was then modelled with demographic characteristics. Chi square statistic was used to assess association between respondent characteristics and knowledge on appropriate medication use during. Strength of association was assessed using odds ratios. Both univariate and multivariate logistic regression analyses were used to test for direction and strength of association between respondent characteristics and self-medication during pregnancy. Analyses were done using STATA 13 at a significant level of p = 0.05.

Ethical Considerations

Voluntary informed consent was obtained prior to recruitment of respondents. Research authorization was obtained from the KNH/U.o.N-Ethics and Research Committee. Confidentiality was ensured by using codes to represent patients instead of names.

Results

The findings of the study were as summarized in the subsequent tables and statements.

Table 1. Baseline characteristics of the respondents.

Characteristic	N = 250	(%)	p value
Age			
<15	2	(0.8)	0.047
15-24	90	(36.)	
25-34	133	(53.2)	
35 and above	25	(10.0)	
Reason for admission			
Normal delivery	126	(50.4)	0.269
Emergency delivery	56	(22.4)	
Medical condition in pregnancy	32	(12.8)	
Obstetric complication in pregnancy	36	(14.4)	
Trimester of pregnancy			
1st trimester	8	(3.2)	0.497
2nd trimester	27	(10.8)	
3rd trimester	215	(86.0)	
Occupation			
Formal employment	3	(1.2)	0.006
Informal employment	34	(13.6)	
House wife	114	(45.6)	
Self-employment	99	(39.6)	
Level of education			
None	16	(6.4)	<0.001
Primary	86	(34.4)	
Secondary	80	(32.0)	
College/university	68	(27.2)	
Residence			
Slum	158	(63.2)	0.876
Middle class	64	(25.6)	
Rural	28	(11.2)	
Previous pregnancies			
0	71	(28.4)	0.366
1	62	(24.8)	
2	63	(25.2)	
3	36	(14.4)	
4	13	(5.2)	
≥ 5	5	(2.0)	

Table 2. Knowledge of the respondents on appropriate medicines use during pregnancy.

Characteristic	N = 250	(%)	p value
Knowledge of pregnancy status			
By Missing periods	170	(68.0)	0.013
By Pregnancy testing	17	(6.8)	
By Feeling symptoms (malaria like)	63	(25.2)	
Knowledge that there are drugs that are dangerous to use during pregnancy			
No	24	(9.6)	0.574
Yes	226	(90.4)	
Source of knowledge			
Pharmacist	41	(16.4)	0.227
Gynaecologist	58	(23.2)	
Nurse	58	(23.2)	
Media	30	(12.)	
Friend/relative	40	(16.)	
Not relevant	23	(9.2)	
Adverse effects of drugs on pregnancy			
Miscarriage	145	(58.)	0.434
Deformation to the foetus	61	(24.4)	
Not sure	44	(17.6)	
Trimester thought to have highest likelihood of teratogenicity			
1st trimester	155	(62.0)	0.931
2nd trimester	14	(5.6)	
3rd trimester	27	(10.8)	
Not sure	54	(21.6)	
Specific drugs stated to be dangerous to use in pregnancy			
Antimalarials in general	59	(23.6)	0.201
Antibiotics in general	13	(5.2)	
Quinine	15	(6.0)	
Chloroquine	5	(2.0)	
Aspirin	9	(3.6)	
Tetracycline	3	(1.2)	
Contraceptives	11	(4.4)	
Not sure	135	(54.0)	
Self-medicated			
No	75	(30.)	
Yes	175	(70.)	
Aware of risks of tobacco and alcohol on pregnancy			
No	136	(54.4)	
Yes	114	(45.6)	
Knowledge Score mean (SD)	6.7	(2.1)	

On univariate analysis, there was significant relationship between knowledge and level of education (p-value< 0.001), age (p-value=0.047) and employment status (p-value=0.006). However, in the multivariable analysis, which adjusted for other factors, only education was

Table 3. Logistic regression for the odds of above average knowledge on self-medication in pregnancy.

Characteristic	Univariable analysis				Multivariable analysis			
	OR	[95% CI]		P>z	OR	[95% CI]		P>z
Age				0.047				
> 35	1.000				1.000			
≥ 35 years	2.626	1.011	6.822		2.412	0.803	7.245	0.117
Reason for Admission				0.269				
Normal delivery	1.000				1.000			
Emergency delivery	1.828	0.950	3.516		1.891	0.927	3.856	0.080
Medical condition	1.207	0.553	2.635		2.100	0.727	6.066	0.170
Obstetric complication	1.475	0.693	3.140		1.845	0.743	4.583	0.187
Trimester of Pregnancy				0.497				
1st trimester	1.000				1.000			
2nd trimester	2.424	0.478	12.302		2.446	0.397	15.087	0.335
3rd trimester	2.228	0.519	9.562		2.965	0.501	17.558	0.231
Occupation				0.006				
Employed (formal/informal)	1.000				1.000			
Self-employment / house wife	0.312	0.136	0.713		0.500	0.196	1.274	0.147
Level of Education				< 0.001				
None / primary	1.000				1.000			
Secondary / college / university	2.772	1.646	4.668		2.238	1.222	4.100	0.009
Place of Residence				0.876				
Slum	1.000				1.000			
Middle class	2.034	1.093	3.784		1.333	0.658	2.701	0.425
Rural	0.644	0.286	1.450		0.650	0.270	1.564	0.336
Previous pregnancies				0.366				
0	1.000				1.000			
1	2.418	1.191	4.908		2.596	1.222	5.515	0.013
2	1.350	0.684	2.666		1.445	0.692	3.020	0.327
3	2.037	0.893	4.647		1.600	0.648	3.952	0.309
4	1.842	0.549	6.183		1.724	0.426	6.971	0.445
≥ 5	0.768	0.121	4.877		0.930	0.121	7.124	0.944

significant for having knowledge (p-value=0.009). The odds of knowledge were 220 % higher for those with secondary, college or university education compared to those with primary education or no education.

Table 4. Self Medication practices during pregnancy

Characteristic	N = 250	(%)
Ever self-medicated during pregnancy		
No	75	(30.)
Yes	175	(70.)
Person consulted on drug use in pregnancy		
Pharmacist	100	(40.0)
Gynaecologist	98	(39.2)
Nurse	47	(18.8)
Herbalist	1	(0.4)
Friend	4	(1.6)
Counselled on drug use in pregnancy		
No	116	(46.4)
Yes	134	(53.6)
Person who counselled		
Pharmacist	30	(12.)
Gynaecologist	36	(14.4)
Nurse	65	(26.)
Friend	3	(1.2)
None	116	(46.4)
Source of drugs used in pregnancy		
Chemist	95	(38.)
Shop	78	(31.2)
None	77	(30.8)
Ever experienced problem with pregnancy		
No	111	(44.4)
Yes	139	(55.6)
Nature of problem experienced		
Deformation of foetus	27	(10.8)
Premature rapture of the membranes	12	(4.8)
Low birth weight	18	(7.2)
Miscarriage	33	(13.2)
Preterm birth	29	(11.6)
Still birth	22	(8.8)
None	109	(43.6)

Table 5. Drugs used for Self-medication in pregnancy

Drug	Frequency	Percentage (%)
Amoxicillin	32	12.8
Paracetamol	75	30.0
Antimalarials	22	8.8
Aspirin	14	5.6
Chlorpheniramine	9	3.6
Antacids	26	10.4
None	72	28.8

Table 6. Use of Prescription Drugs during pregnancy

Characteristic	N = 250	(%)	p value
FDA categories of drugs prescribed			
Not applicable	64	(25.6)	
B	109	(43.6)	
C	65	(26.)	0.109
D	11	(4.4)	
X	1	(.4)	
Number of the drugs Prescribed			
Zero	64	25.6	
One	31	12.4	
Two	37	14.8	
Three	39	15.6	0.673
Four	22	8.8	
Five	26	10.4	
> Five	31	12.4	

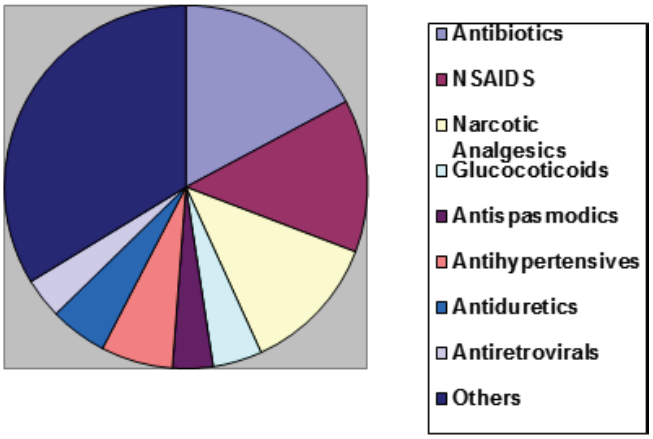

Figure 1. Pharmacological Classes of drugs prescribed in pregnancy

Discussion

Research has shown that the level of knowledge of a woman has an important bearing on their ability to understand their treatment and thus seek to improve its outcomes (11). It was therefore a key objective of this study to find out what factors influence the level of knowledge of the respondents on drug use in pregnancy and then relate the level of knowledge to the appropriateness of their use of medications while pregnant. Appropriate use of medicines in pregnancy was defined as not self-prescribing while pregnant whereas inappropriate use was self-medication in pregnancy.

After adjusting for all the other variables by a logistic regression model, it was evident that only level of education (p= 0.09) was significantly influencing the level of knowledge of the women and hence their drug use practices during pregnancy. This finding is in contrast with the findings of a study carried out in Italy which reported that older women, better educated women and those who reported health problems were at a higher risk of using drugs for self-medication (8).

Drugs mostly used for self-medication during pregnancy were Paracetamol (30%), Amoxicillin (12.8%), Antacids (10.4%), Antimalarials (8.8%), Aspirin (5.6%) and Chlorpheni-

ramine (3.6%). Just like it was evident from this study, paracetamol is the most widely used analgesic in pregnancy. Although there is no known association with teratogenicity, there is little evidence to support the lack of association (13).

In Kenya, amoxicillin is classified as a prescription only medicine. Despite such classification, the respondents who reported to have used the drug for self-medication stated that they obtained it from chemists without a prescription. However, a population based study of maternal use of amoxicillin and pregnancy outcome in Denmark (14), did not find any increased risk of adverse pregnancy outcome.

Antimalarials were often not specified, leaving the risk of having used teratogenic ones like quinine in the third trimester. However, despite fear of potential toxicity limiting antimalarial drug use in pregnancy, there is no evidence to suggest that at standard doses, any of the antimalarial drugs is teratogenic (15).

Twenty-eight per cent of the respondents reported having used no drug at all for self-medication during pregnancy. This result was obtained based on a simple question; "During your current pregnancy, have you ever used self-medication?" The author did not analyse their level of education because it was thought that the accuracy of responses to this question was only pegged on recall and not much literacy. Different studies have shown that 40-90% of pregnant women take at least one drug during pregnancy (4, 5, 16) and that many women are exposed to several drugs (17).

On average, 2.72 drugs were prescribed for each respondent. Most prescriptions (15.6%) had three drugs. In a similar study done in Ethiopia, 71.3% of women interviewed were prescribed at least one drug during pregnancy. Most of the drugs prescribed were iron and supplements followed by anti-infectives. Nearly 4% of the pregnant women were prescribed drugs from category D or X of the FDA risk classification (18).

Antibiotics were the most prescribed class of drugs (17.2%). This is probably because the study was carried out in a hospital within a tropical country where the prevalence of infections is high. It is also possible that prescribing of antibiotics was irrational in many cases. If the latter scenario is true this would contribute to development of resistant strains of the microorganisms targeted by the prescribed drugs. Equally widely prescribed were NSAIDS (13.6%), Narcotic analgesics (12.4%) and anti-hypertensives (6.4%). Anticonvulsants (0.8%) and antifungals (0.8%) were the least prescribed classes. Up to 25.6% of the patients interviewed were discharged without prescribing any drug to them.

Most drugs prescribed (43.6%) belonged to FDA category B. No drug from category A was prescribed to any of the respondents whereas 4.4% of the respondents got a prescription with a drug of category D. One category X drug was prescribed to one patient only. 25.6% of the respondents were attended to and discharged without the use of any prescription drug. These patterns of prescription in pregnancy possibly explain the level of risk that the prescribers are willing to take based on the potential benefits of the prescribed medications to the mother and foetus. This is probably why category B drugs were the most prescribed as they are safe and many. On the other hand category A drugs are very few hence their chance of being prescribed over the short period of the study is equally low. The one category X drug prescribed was certainly an error in prescription. However, the author did not manage to follow up on the gestational outcomes due to time and budget constraints. The category D drugs that were prescribed were probably those that promised much higher benefits than the risks they posed and alternatives were not available. In the Ethiopian study cited above (18), 71.3% of women interviewed were prescribed at least one drug during pregnancy. Majority of drugs prescribed were, iron and mineral supplements followed by antibiotics. Nearly 4% of the pregnant women were prescribed drugs from category D or X of the FDA risk classification (18). FDA categorizes medicines based on their safety of use in pregnancy thus guiding users on which ones to avoid in pregnancy (19). The author was not able to trace retrospectively and find out why the category X drug was prescribed and the pregnancy outcome thereof. According to a study done in Pakistan in 2008, all the pregnant women attending the ante natal clinics received a prescription containing at least one drug. 55.4% of the prescriptions were issued in the third trimester, 33.6% in the second and 11.0% in the third trimester (20). These findings mirror the reports from a cohort study conducted to determine the correlates of prescription drug use during pregnancy which reported that most of the pregnant women were prescribed a category B drug (56%), and 4% of women were prescribed a category D or X drug. The most common classes of medications prescribed were antibiotics (62%), analgesics (18%), asthma medications (18%), and antiemetics (17%) (21).

Conclusions and Recommendations

These findings provide sufficient scientific evidence to conclude that the level of education and hence the level of knowledge on drug use in pregnancy of a woman is the single most important factor that significantly influences their self-medication practices while pregnant. Improving the level of education of a woman therefore improves not only their health but also those of their offspring by lowering the chances of in utero exposure to potentially teratogenic drugs. A national and regional survey on medication use in pregnancy is necessary since currently, there are very few studies in this topic carried out within East Africa. A further research to analyze the rationale for prescription medication use during pregnancy, especially antibiotics, is warranted by the findings of this study. Such a study should include a longitudinal component to assess gestational outcomes following exposure to various FDA categories of medications. A local prospective and interventional study on this topic would be useful in unearthing correlates of gestational outcomes in our setting. There is need for a concerted campaign against inappropriate medicines use in pregnancy as this would improve maternal and child health. Pharmacovigilance efforts also need to be increased with a focus on drug use in pregnancy.

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Accuracy of Splitting of Carbamazepine Tablets Available in the Kenyan Market

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Abstract

Carbamazepine is an example of a drug with a narrow therapeutic index (NTI) whose dose response should be carefully titrated to avoid adverse effects associated with over- or under-dosages. Currently, there are no studies in Kenya that have investigated the accuracy of splitting tablets of such drugs. Carbamazepine tablets available in Kenya are scored, indicating suitability for splitting.

This study set out to determine the uniformity in weight of half tablets of a number of brands of carbamazepine 200mg

tablets, the loss in mass upon splitting, and the accuracy of splitting tablets by hand and by means of a knife.

Twenty tablets each of 5 different brands were split by hand and using a knife. The uniformity in weight of the halves obtained was compared as well as the accuracy of the splitting method.

It was found that none of the half tablets passed the adopted United States Pharmacopeia (USP) test for Uniformity in Weight, whether split by hand or using a knife. Eighty-seven (87%) half tablets obtained from splitting by hand passed the European Pharmacopeia (Ph. Eur.) test for Subdivision of Tablets while only 52 half tablets passed the USP test for Uniformity of Dosage Units. When tablets were split by means of a knife, 81 (81%) half tablets passed the Ph. Eur. test while only 34% of the half tablets passed the USP test. Loss in mass for majority of the products was less than 3%.

Splitting of tablets results in variations in weight of half tablets. The USP test is stricter compared to the Ph. Eur. Test with the majority of the half tablets satisfying the Ph. Eur. requirements. Splitting by hand gave better results than using a knife. However, due to weight variation of halves, splitting of carbamazepine tablets is not recommended.

Keywords: *NTI - drugs, tablet splitting, half tablets, uniformity in weight, carbamazepine 200mg scored tablets.*

Introduction

Tablet splitting involves division of tablets of higher strength into lower strength halves (or quarters) to provide the patient with the appropriate dose. Tablets may be divided for ease of swallowing for pediatric and geriatric patients . However, accuracy of splitting only becomes important when the aim is to give less than the whole of the tablet. Tablets may also be divided to reduce costs for the patient, since for many drug products the cost of different dosage strengths is equivalent .

The US Food and Drug Administration (FDA) requires that the dosage amount meant to be administered after splitting should not be below a minimum therapeutic dose indicated on the approved labeling. However, there are no specific tests stipulated to ascertain this.

Tablets are split either by hand or by use of a splitting device such as a knife, a razor, a pair of scissors or a tablet-splitter . Tablet splitters and other devices have been shown to give unequal doses and their accuracy depends on the type of splitters, tablet or operator . It has been shown that splitting of tablets is not accurate and results in weight variation, content variation and significant loss in mass . For drugs with a wide therapeutic index, the risks associated with tablet splitting are less significant. A study on levothyroxine, a drug with a narrow therapeutic index (NTI), indicated problems such as non-optimal dose, drug interactions and need for drug-monitoring for toxicity . The same study defined NTI-drugs such as carbamazepine as drugs with less than two-fold difference in the minimum toxic concentration and minimum effective concentration in the blood. Uniformity studies in the country have only been undertaken for whole tablets and not halves or quarters. Furthermore, the current pharmacopoeias do not contain specific tests for half tablets and as such only adopted tests can be applied. This study aimed to evaluate the accuracy of splitting carbamazepine 200mg scored tablets available in the Kenyan market. The uniformity in weight of half tablets and the loss in mass on splitting were determined based on adopted USP and Ph. Eur. standards. Accuracy of splitting of tablets by hand and using a knife was compared as well.

Methods

The study applied a laboratory-based experimental design. Five brands of carbamazepine 200mg scored tablets were selected for the study. The brands selected were determined based on their availability in pharmacies in Nairobi Central Business District, Kenya. Four widely available brands were purchased from retailers. These were Tegretol®, Neurotrol®, Carbazina®, and Storilat®. A fifth brand, Mazapine®, was obtained from Mathari National Hospital, the largest mental healthcare facility in the country; Mazapine® was not available in retail pharmacies. Twenty tablets of each of the given brands were investigated, totaling to one hundred tablets.

The study was carried out at the Science Laboratories of Kenyatta University, Main Campus. The tablets were weighed while intact using an FA-2104 electronic analytical balance. For each brand, half of the tablets were split by hand and the other half using a knife. A single male volunteer, a fifth year Bachelor of Pharmacy student, was used to split tablets to ensure reproducibility of the results. It abolished personal variation that would be encountered when using multiple volunteers considering the small sample size. When splitting by hand, the student was advised to hold the tablet sideways between the right-hand thumb and forefinger and apply pressure while placing the tablet on the left palm. A common kitchen knife purchased from a national supermarket chain was used to split the tablets. When splitting using a knife, the student was directed to place the tablet on a surface with the score line facing upwards. Pressure was placed on the blunt edge of the knife using the left hand while the sharp edge was placed directly on the score line and splitting directed by the right hand on the knife handle. The half tablets obtained were weighed and their weights recorded.

Results

The performance of the tablet halves on testing for uniformity in weight based on both the USP and Ph. Eur. tests gave variable results when tablets were split by hand (Table 1) or using a knife (Table 2).

To assess amount and acceptability of variations, the relative standard deviation as a percentage (%RSD) of half tablets weights per brand was calculated as follows:

%RSD= (SD/mean) *100%

The expected weight of each tablet was calculated as follows:

Target weight = sum of half tablets of each brand/number of half tablets of each brand

Based on the target weight calculated above, a percentage by weight was calculated to determine whether the range fell within pharmacopoeia standards as follows:

Percentage of target weight range (% target wt.) = (measured weight/target weight) *100%

Table 1. Weight uniformity analyses of tablet halves obtained from hand splitting

Brand®	% RSD	% target wt. range	No. outside USP requirements (%)	Remark	No. outside Ph. Eur. Requirements (%)	Remark
Carbazina	21.98	47.5-150.7	13(65)	Fail	10(50)	Fail
Mazapine	5.16	86.4-110.4	5(25)	Fail	0(0)	Pass
Neurotrol	9.66	70.7-126.5	5(25)	Fail	2(10)	Fail
Storilat	5.89	88.2-108.8	10(50)	Fail	0(0)	Pass
Tegretol	23.62	86.4-114.4	15(75)	Fail	1(5)	Pass
TOTAL	-	-	48(48)	-	13(13)	-

Table 2: Weight uniformity analyses of tablet halves obtained from splitting using a knife.

Brand®	% RSD	% target wt. range	No. outside USP requirements (%)	Remark	No. outside Ph. Eur. Requirements (%)	Remark
Carbazina	21.25	44.2-122.6	14(70)	Fail	4(20)	Fail
Mazapine	20.33	61.8-136.7	15(75)	Fail	10(50)	Fail
Neurotrol	6.49	88.2-114.2	8(40)	Fail	0(0)	Pass
Storilat	13.48	68.9-130.2	18(90)	Fail	2(10)	Fail
Tegretol	10.18	80.7-114.4	11(55)	Fail	3(15)	Fail
TOTAL	-	-	66(66)	-	19(19)	-

The loss in mass that occurred on splitting the products by hand and using a knife is shown in Table 3 and Table 4, respectively.

The loss in mass in grams was calculated as follows:

Loss in mass (g)= Intact weight in grams - Sum of mean weight of halves in grams

The loss in a mass as a percentage was calculated as follows:

% Loss = (loss in mass/intact weight in grams) *100%

Table 3. Loss in mass on splitting carbamazepine 200mg tablets by hand.

Brand®	Intact wt. (g)	Mean Wt. of greater half (g)	Mean Wt. of lesser half (g	% loss	Remarks)
Carbazina	0.2774	0.1544	0.1187	0.22	Pass
Mazapine	0.2768	0.1422	0.1331	0.76	Pass
Neurotrol	0.2836	0.1482	0.1355	0.14	Pass
Storilat	0.2608	0.1371	0.1234	0.07	Pass
Tegretol	0.2840	0.1526	0.1303	0.31	Pass

Table 4. Loss in mass on splitting carbamazepine 200mg tablets with a knife.

Brand®	Intact wt. (g)	Mean Wt. of greater half (g)	Mean Wt. of lesser half (g	% loss	Remarks)
Carbazina	0.2782	0.1499	0.1242	5.10	Fail
Mazapine	0.2722	0.1597	0.1147	1.21	Pass
Neurotrol	0.2863	0.1498	0.1334	0.14	Pass
Storilat	0.2602	0.1436	0.1157	0.29	Pass
Tegretol	0.2837	0.1515	0.1282	1.64	Pass

Discussion

The present work focused solely on weight variation without assessing content uniformity but assay was not feasible at the time of the study. Weight uniformity can be used to predict the uniformity in content assuming uniform distribution of the drug. Five brands were chosen as these were the ones widely available in retail pharmacies within Nairobi city, Kenya at the time of the study. The study also applied a sample size that was economically feasible at the time.

Half tablets of NTI-drugs have been shown to perform poorly when tested for uniformity in weight . The adopted USP specifications have also been shown to be stricter than those of the Ph. Eur. and this explains why more products were able to meet Ph. Eur. requirements . The adopted USP specifications are based on the standards set for whole tablets as there are no specifications for half tablets yet. The half tablets are expected to have a variation in weight within the range of 95-105% of the expected weight for NTI-drugs. The Ph. Eur. Test for subdivision of tablets gives a range of 85-115% for split tablets to pass.

All the products failed the adopted USP test for Uniformity in Weight of half tablets whether split by hand (Table 1) or by means of a knife (Table 2). Three products, when split by hand, passed the Ph. Eur. test for Subdivision of Tablets (Table 1) compared to when split using a knife where only one product passed (Table 2). Splitting using a knife gave great variations, for instance, the half tablets of Carbazina® contained as little as 47% of the expected weight and as much as 150% per half (Table 2), predicting chances of under and overdoses. Variation was also seen with half tablets of Mazapine® with a range of 61.8% to 136.7% and Storilat® ranging from 68.9% to 130.2% from expected target weight (Table 2).

Loss in mass directly reflects on the accuracy of the dosage the patient receives. Friability affects the extent of loss in mass on splitting tablets . Based on a proposed mean loss in mass of not more than 3% , majority of the products showed acceptable powdering and subsequent loss in mass after splitting whether by hand or using a knife (Table 3 and 4). The only exception was Carbazina® tablets split using a knife which showed a loss in mass of greater than 3% (Table 4). On comparing the weights of the halves obtained, half tablets of Carbazina® obtained from splitting by hand also showed the greatest difference, posing a risk of variable dosing (Table 3). When split using a knife, Mazapine® half tablets split using a knife showed the greatest difference in weight. This could result in a possibility of non-uniform dosing especially when

the aim is to give less than the whole tablet. Varying results may be obtained from content uniformity tests as these results focus on loss in mass of the tablet and not loss of the active drug.

In this study, it was found that splitting tablets by hand was more accurate than splitting tablets using a knife. Splitting by hand ensures the tablet is held firmly in position during splitting. Two of the products split by hand passed the Ph. Eur. test for Subdivision of Tablets while only 1 product split by means of a knife passed the test. On the contrary, another study found splitting tablets by means of a knife to be more accurate . This finding may be attributed to the size and hardness of the tablets being investigated. Smaller and harder tablets may be more difficult to split accurately by hand. In this study, however, half tablets obtained from splitting by hand gave the least deviation from the theoretical intact weight. Studies show that it may be painful and difficult to break tablets by hand. This is especially true for persons with impaired hand function such as the elderly or arthritic patients. Devices such as tablet splitters were not applied in this study due to their lack of availability in most facilities within the country.

Other problems may arise with tablet-splitting such as inability of patients to interpret half-tablet prescriptions correctly. The patient may assume their tablets have already been split and take whole tablets or if the tablets were split before dispensing, the patient may re-split them. In addition, when the unused portion of split tablets is returned to the prescription bottle or envelope, tablet fragments can continue to crumble resulting in loss of mass. Patients may also just get tired of splitting tablets and stop taking their medication.

With respect to the operator, various individuals may have difficulty splitting tablets due to either age or hand deformities. Elderly patients, for instance, may find it challenging to split tablets into perfect halves due to factors such as hand dexterity and impaired vision. However, one of the aims of this study was to compare splitting devices and as such a "best case" operator was used to reduce personal variability in results.

Results from the current work indicate that dividing carbamazepine tablets does not guarantee accurate dosing. The potential source of inaccuracy could be significant in clinical settings and have an impact on clinical outcomes. These variations in weight of half tablets show that the presence of a score line does not necessarily qualify a tablet suitable for splitting.

Powdering may lead to sub-therapeutic doses and consequently affect clinical outcomes. Majority of the selected products, however, showed minimal loss in mass on splitting. Equal daily doses are determined by the ability of the patients to split the tablets in perfect halves.

Recommendations

When splitting of tablets is inevitable, tablets should be split by hand as this gave better results. Different brands of a drug may have varying pharmaceutical characteristics and consistent breakability should not be assumed across products; individual tests must be performed. Products should be subjected to the adopted USP test for Uniformity in Weight pending its official inclusion into the Pharmacopoeia which is stricter and thus ensures greater accuracy.

Further areas of research on this topic would include content uniformity tests to evaluate the effect of splitting on dosage accuracy. A study into other aspects of tablet splitting such as friability, shape and hardness of tablets can also be done to determine their effect. Multiple volunteers from different age groups may also be used to investigate the effect of age and gender on the accuracy of splitting tablets.

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Prevalence of Adverse Events of Anti-Tuberculosis Drugs and their Impact on Adherence to Treatment in Nairobi City County

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Abstract

Background

Tuberculosis is a global health problem and Kenya is among the countries with high burden of the disease. The disease is curable but the drugs used have several adverse effects which increase the morbidity and mortality. They also affect adherence to treatment.

Objective

To determine the prevalence of adverse drug events of first line anti-tuberculosis therapy and their impact on adherence to treatment in Nairobi City County.

Methods

The study was carried out in nine health facilities in Nairobi City County. A cross-section study design was used targeting adult patients on first line anti-tuberculosis drugs. A sample of 190 participants was selected using simple random sampling. Eligible respondents were taken through a consenting process and those who concurred were included in the study. Data was collected using a researcher-administered questionnaire. The participants were interviewed and their responses entered accordingly. Analysis of the data was done using STATA version 13 and both inferential and descriptive analysis were used to generate the report.

Results

115(60.53%) respondents were males and 48(25.26%) had HIV coinfection. The most common adverse drug events were; nausea, vomiting, anorexia, tiredness and weakness, numbness and burning sensation in the limbs, clumsiness or unsteadiness, depression, skin rash, arthralgia, blurred vision and eye pain. The majority (51.58%) of the respondents had high adherence to anti-tuberculosis drugs. There was a statistically significant relationship between the level of adherence and duration of treatment (p=0.05); alcoholism (p=0.002); depression (p=0.026).

Conclusion

Males are more predisposed to tuberculosis than females and adverse drug events are common in patients on treatment.

Key words: *Adherence, Anti tuberculosis drugs, Adverse drug events*

Introduction

Kenya is among the countries with high tuberculosis burden in Africa with a prevalence of 558 per 100,000 people (1). The disease is more common in men between the ages of 25 and 34 years, urban dwellers, and women over the age of 65 years. Tuberculosis is curable and the willingness of a patient to comply with prescribed regimens

is the mainstay of treatment (2). Several factors influence patients' compliance with treatment. Adverse drug events play an important role and they are common when drugs are taken frequently, in combination and over prolonged periods. There is a high level of under-reporting of actual and suspected adverse drug reactions (ADRs) but they are significant factors in the treatment of chronic conditions like tuberculosis (3). Adverse drug reactions can cause considerable morbidity and mortality (4). These events may incur substantial additional costs because of added outpatient visits, tests, and hospitalizations. The frequency, severity, and the nature of tuberculosis therapy induced ADRs have always been a concern to patients and health workers (5). The overall incidence of adverse drug reactions ranges from 5.1% to 83.5% (6). In Nairobi, the incidence of adverse drug events due to anti-tuberculosis drugs has not been adequately explored. There is no regular monitoring of adverse drug reactions due to tuberculosis chemotherapy and patients present in the health facilities occasionally with severe signs and symptoms. The objective of this study was to determine the prevalence of adverse events and their impact on adherence to first line anti-tuberculosis drugs in Nairobi City County.

Methods

A cross-section design was used and all patients suffering from tuberculosis in Nairobi City County were targeted. The study population comprised of those patients attending Kayole I, Kayole II, Umoja, Dandora I, Dandora II, Ruai, Njiru, Kariobangi South and Kariobangi North health centers. Participants enlisted in the study were at least 18 years of age, on first line anti-tuberculosis drugs for at least one month, able to communicate effectively and consented to participate in the study. One hundred and ninety participants were selected using simple random sampling where a coin was tossed and whoever scored the head was included to participate in the study after consenting. At least fifteen participants were selected from each health facility depending on the number of available participants. Data was collected using researcher administered questionnaire. The HIV status of the participants was obtained from the respective medical records. The participants were invited for a face to face interview and data entered into a structured questionnaire with coded responses. This was done in a place within the health facility where only the researcher and the participant were present to ensure confidentiality of the respondents. The questionnaire had three main sections, namely; sociodemographic characteristics, adverse events and adherence to drugs. Adherence was assessed using the 8 point Morisky adherence scale. Prior to the study approval was obtained from Kenyatta National Hospital–University of Nairobi ethical Research Committee and permission to access the patients' records was given by the administrator of the respective health facilities. Data were entered into an excel sheet and exported to STATA version 13. Both descriptive and inferential statistics were used to analyze the data which was summarized in charts and tables.

Results

Sociodemographic characteristics

The majority one hundred and fifteen (60.53%) of the respondents were males and 103(54.21%) had spouses (Table 1). 56(29.47%) participants had a body mass index below 18.5 and therefore underweight.

Table 1. Sociodemographic characteristics (N=190)

Variable	Frequency	Percent
Sex		
Male	115	60.53
Female	75	39.47
Marital status		
Married	103	54.21
Single	87	45.79
Age category		
18-30	84	44.21
31-40	69	36.32
Above 40	37	19.47
BMI		
Below 18.5	56	29.47
18.6- 25	116	61.05
Above 26	18	9.48
Highest education level		
No formal education	2	1.05
Primary	64	33.68
Secondary	88	46.32
Tertiary	36	18.95
HIV Co-infected	48	25.26
Relapsed TB infection	16	8.42
Diabetes mellitus	5	2.63
Alcoholism	102	53.68
Tobacco smoking	67	35.26

Among the participants, 37(19.47%) were above forty years of age and 36(18.94%) had a tertiary level of education. 48(25.26%) respondents were infected with HIV while 16(8.42%) had a previous episode of active tuberculosis. 67(35.26%) and 102(53.68%) respondents used to smoke and take alcohol respectively before diagnosis and initiation of treatment.

The participants were at different stages of treatment as shown in figure 1 below. Seventy three (38.42%) participants were on four drugs during the first two months of the intensive phase of therapy. The continuation phase where two drugs (isoniazid and rifampicin) were administered commenced from the third month of treatment and 117(61.57%) respondents were involved.

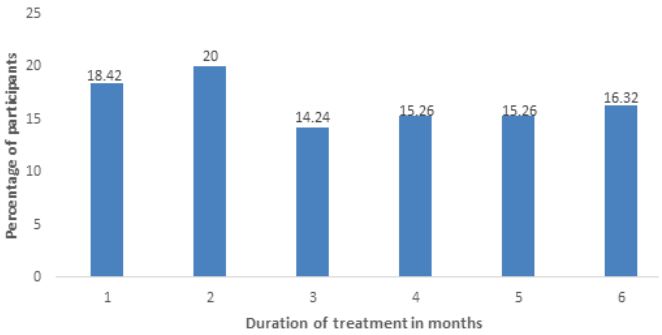

Figure 1. *Distribution of respondents according to duration of treatment (N=190)*

Prevalence of adverse drug events

The most common adverse drug events were neuropsychiatric, immunological and gastrointestinal disturbances (Table 2). Among those with gastrointestinal side effects, 59(31.05%) complained of nausea and vomiting while 58(30.53) were anorexic. Neuropsychiatric side effects manifested in several ways and among the victims, 99(52.11%) complained of tiredness and weakness, 70(36.84%) experienced numbness of extremities, 32(16.84%) had burning sensations, 38(20%) complained of clumsiness or unsteadiness, while 61(32.11%) had tingling sensations in the limbs and 14(7.3%) were depressed. Among the musculoskeletal disturbances, 58(30.53%) participants had a skin rash, 69(36.32%) complained of arthralgia. 38(20%) had blurred vision while 17(8.85%) complained of eye pain.

Table 2. Prevalence of adverse drug events (N=190)

Adverse drug events	Frequency	Percent
Gastrointestinal disturbances		
Loss of appetite	58	30.53
Nausea and vomiting	59	31.05
Neuropsychiatric disturbances		
Tiredness/ weakness	99	52.11
Clumsiness/unsteadiness	38	20
Numbness	70	36.84
Tingling sensation	61	32.11
Burning sensation or pain in the hands and feet	32	16.84
Mental depression	14	7.37
Psychosis	3	1.58
Seizures	2	1.05
Hematological disturbances		
Sore throat	14	7.37
Unusual bleeding and bruising	3	1.58
Musculoskeletal disturbances		
Skin rash	58	30.53
Arthralgia	69	36.32
Muscle twitching	3	1.58
Visual disturbances		
Blurred vision	38	20
Inability to distinguish green and yellow	3	1.58
Eye pain	17	8.95
Others		
Decreased or increased urine	48	25.26
Increased thirst	36	18.95

Level of adherence to drugs

The level of adherence to tuberculosis treatment was determined using the Morisky eight-point scale and the results are summarized in fig 2.

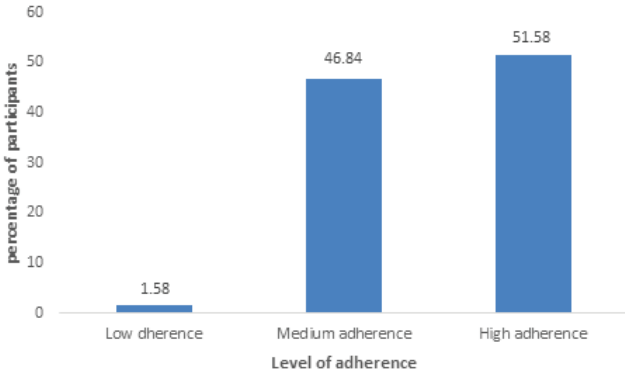

Fig 2. *Level of adherence to anti-tuberculosis drugs (N=190)*

High adherence was reported among 98(51.58%) respondents and 89(46.84%) had medium adherence. Only 3(1.58%) respondents had a low level of adherence.

Association between sociodemographic characteristics and level of adherence

Using Fisher's exact test the relationship between sociodemographic characteristics and level of adherence to TB drugs was explored and the results are shown below in Table 3. 57(49.57%) males and 32(42.67%) females exhibited medium adherence compared to 57(49.57%) and 41(54.67%) who had high adherence respectively but the difference was statistically insignificant (p=0.459). Participants across all age groups mainly showed medium and high adherence with no significant difference. A statistically significant association existed between duration of therapy and level of adherence (p=0.05). The level of adherence generally decreased in the third month, then went up towards the end of treatment. History of drinking alcohol was significantly associated with adherence (p=0.002).

Table 3. Association between sociodemographic characteristics and level of adherence

Characteristic	Level of adherence			
	Low (n, %)	Medium (n, %)	High (n, %)	P value
Sex				
Male	1(0.86)	57(49.57)	57 (49.57)	0.459
Female	2(2.67)	32(42.67)	41 (54.67)	
Age in years				
18-30	2 (1.05)	37 (19.47)	45 (23.68)	0.572
31-40	1 (0.53)	37 (19.47)	31 (16.32)	
Above 40	0 (0)	15 (7.89)	22 (11.58)	
Marital status				
Married	2 (1.05)	42 (22.11)	49 (25.79)	0.159
Single	1 (0.53)	47 (24.74)	39 (20.53)	
Education level				
Primary	1 (0.53)	32 (16.84)	33 (17.37)	
Secondary	1 (0.53)	40(21.05)	47 (24.74)	0.788
Tertiary	1 (0.53)	17 (8.95)	18 (9.47)	
Employment status				
Formal	0 (0)	21 (11.05)	17 (8.94)	0.468
Non formal	3 (1.58)	68 (35.79)	80 (42.11)	
Duration of treatment				
1	0 (0)	12 (6.32)	23 (12.11)	
2	0 (0)	18 (9.47)	20 (10.53)	
3	1(0.53)	16 (8.42)	11 (5.79)	**0.05***
4	2 (1.05)	18 (9.47)	9 (4.74)	
5	0 (0)	10 (5.26)	19 (10)	
6	0 (0)	15 (7.89)	16 (8.42)	
HIV infection	2 (4.17)	21(43.75)	25 (52.08)	0.249
Previous TB infection	0 (0)	8 (50)	8 (50)	1
Malnutrition	0 (0)	8 (44.45)	10 (55.56)	0.859
Diabetes mellitus	0 (0)	1(0.25)	4 (0.75)	0.420
Alcoholism	0(0)	58 (56.86)	44 (43.14)	**0.002***
Tobacco smoking	0(0)	34 (50.75)	33 (49.25)	0.443

*- statistically significant relationship

Association between adverse drug events and adherence

Table 4. Association between adverse drug events and level of adherence. (***See Next page)***

Adverse event	Adherence level			p value
	Low (n, %)	Medium (n, %)	High (n, %)	
Gastrointestinal disturbances				
Loss of appetite	1(1.72)	29 (50)	28 (48.28)	0.837
Nausea and vomiting	1 (1.69)	30 (50.85)	28 (47.46)	0.789
Neuropsychiatric disturbances	2(2)	52 (52.53)	45 (45.45)	0.184
Tiredness and weakness	1 (2.63)	20 (52.63)	17 (44.74)	0.385
Clumsiness and unsteadiness	1 (1.43)	38 (54.29)	31 (44.29)	0.221
Numbness	1(1.64)	32 (52.45)	28 (45.9)	0.532
Tingling sensation	0 (0)	16 (50)	16 (50)	0.912
Burning sensation or pain in the hands	1(7.14)	10 (71.4)	3(21.43)	0.026*
Mental depression	0 (0)	2(66.7)	1(33.3)	0.946
Psychosis	0	2(100)	0	0.250
Seizures				
Musculoskeletal disturbances				
Skin rash	0 (0)	30 (51.72)	28 (48.28)	0.515
Arthralgia	1 (1.45)	33 (47.83)	35 (50.72)	0.946
Visual disturbances				
Formal	0	19 (47.37)	21(52.63)	1
Non formal	0	7 (41.18)	10 (58.82)	0.713
Others				
Change in volume and frequency of urination	1(2.08)	22(45.84)	25 (52.08)	1
Increased thirst	1(2.78)	15(41.67)	20(55.56)	0.498

- statistically significant p-value

Association between adverse drug events and adherence

The association of adverse drug events and adherence to anti-tuberculosis drugs is shown in table 4. Among those participants who experienced nausea and vomiting, 29(50%) and 28(48.28%) had a medium and high level of adherence respectively and only 1(1.72%) depicted low adherence.

Nausea and vomiting occurred in participants having 30(50.85%) and 28(47.46%) medium and high adherence respectively. Despite that these gastrointestinal disturbances were common there was no statistically significant association as all the p values were greater than 0.05. Majority of participants who suffered neuropsychiatric disturbances portrayed the medium and high level of adherence. Among the participants suffering from tiredness and weakness, 52(52.53%) and 17(45.45%) showed medium and high adherence respectively and the trend was similar among

Those who presented with tingling and burning sensation in the limbs but no statistically significant association was observed. Mental depression was significantly associated with the level of adherence (p=0.026) and the majority 10(71.43%) had medium adherence. Skin rash manifested in 30(51.72%) and 28(48.28%) participants with medium and high adherence respectively.

Discussion

The risk of progression from exposure to the tuberculosis bacilli and development of the active disease is a two-stage process governed by both exogenous and endogenous risk factors (7). Exogenous factors play a key role in enhancing the progression from exposure to infection among patients where the bacillary load in the sputum and the proximity of an individual to an infectious TB case are key factors. Similarly, endogenous factors facilitate progression from infection to active TB disease. Majority of the participants were males as has been observed in several studies. Possible reasons for higher predisposition among males include differences in immunity, more frequent external contacts for men than women and differences in health-seeking behavior. Over half of the respondents were married and had a history of drinking. Alcohol has been recognized as a strong risk factor for TB disease (8), and meta-analysis studies have established that it is a risk factor for clustering (or recent transmission of TB) in both high and low-incidence countries(9). Reasons for this occurrence are an alteration in the immune system, specifically change in the signaling molecules responsible for cytokine production (10). About thirty-five percent were smoking before diagnosis and initiation of treatment. The relative risk of TB disease is high among smokers in comparison to nonsmokers and there is increased risk of death in persons with active TB. Biological explanations include impaired clearance of mucosal secretion (11), reduced phagocytic ability of alveolar macrophages (12) and decrease in the immune response and/or decreased CD4 + due to the nicotine in the cigarettes are reasons for increased susceptibility to pulmonary tuberculosis. Approximately a quarter of respondents were HIV infected which exacerbates the severity of tuberculosis (13). Cell-mediated immunity is a crucial component in the host defense against M. tuberculosis that is weakened by HIV infection resulting in increased risks in reactivation of tuberculosis which also accelerates HIV progression through increased systemic immune activation. Therefore, coinfection increases the rate of disease progression and mortality among patients (14). A few participants had diabetes mellitus which increases the risk of active tuberculosis. Diabetes directly impairs the innate and adaptive immune responses, thereby accelerating the proliferation of tuberculosis. Decreased production of IFN-γ and other cytokines diminishes T-cell immunity and reduces chemotaxis in neutrophils (15) and are thought to play a role in increasing the propensity of diabetic patients to developing active tuberculosis.

Gastrointestinal side effects were experienced by about a third of the respondents. They included loss of appetite, nausea, and vomiting. The drugs which are responsible for these side effects are pyrazinamide and rifampicin. The prevalence was lower than what was observed in Nepal where it was 48.6%(16). Neurological adverse events manifested as unsteadiness, numbness, tingling sensations, depression and psychosis. Isoniazid may be the responsible

drug for this side effect since it is a competitive inhibitor of pyridoxine. Visual disturbances characterized by blurred vision, eye pain and inability to distinguish yellow and green color were probably caused by ethambutol since it damages the retina. Arthralgia occurred in over a third of cases with similar findings (16) and most likely due to pyrazinamide that causes accumulation of uric acid.

The rate of adherence to treatment for tuberculosis was high, a trend similar to that reported by Tesfahuneygn and co-workers (17). This suggests that the counseling done in the clinics was adequate. Bivariate analysis showed that mental depression, duration of treatment and history of taking alcohol affected the level of adherence. Depressed people had adherence while those with a history of alcoholism had medium adherence. Adherence decreased as the duration of treatment increased.

Conclusion

Tuberculosis is more common in males than females. The most common adverse drug events involved gastrointestinal, neuropsychiatric and musculoskeletal systems. Adherence to medications was high among depressed respondents and decreased with an increase in the duration of treatment.

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Adverse Drug Reactions Among Patients Being Treated For Multi-Drug Resistant Tuberculosis In Nairobi City County Health Facilities

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Abstract

Background

Increased incidence of Multidrug-resistant tuberculosis (MDR-TB) is eroding the gains made in controlling the disease. The drugs used to treat MDR-TB have several side effects which enhance morbidity and mortality associated with the disease.

Objective

To determine the prevalence of adverse drug events among patients on MDR-TB therapy in Nairobi City County.

Methods

A longitudinal study was carried out in four health facilities within Nairobi City County. It involved twenty- three participants who were on MDR-TB treatment selected through universal sampling. Eligible respondents were taken through a consenting process and those who concurred were included in the study. Data was collected using a researcher-administered questionnaire. The participants were interviewed and their responses entered accordingly. Analysis of the data was done using STATA version 13 and both inferential and descriptive analyses were used to generate the report.

Results

Among the patients who were on therapy for drug-resistant tuberculosis, the main adverse drug events involved disturbances of the nervous system (91.3%), gastrointestinal (87%), musculoskeletal (73.9%), cardiovascular (43.5%) and endocrine (43.5%) systems. The other less common but serious adverse drug events were nephrotoxicity (6, 21.6%), hepatotoxicity (5, 21.7%) and rash (5, 21.6%). All the participants suffered from many adverse events and 12(52.2%) had experienced ten and below while 11(47.8%) had more than ten adverse events.

Conclusion

MDR –TB therapy causes several adverse events involving most body systems.

Key words: *MDR-tuberculosis, Adverse drug reactions.*

Introduction

Multi-drug resistant tuberculosis (MDR-TB) describes the disease caused by Mycobacterium tuberculosis strains that are resistant to at least isoniazid and rifampicin (1). Globally, MDR-TB is a threat to the gains made in the control of tuberculosis. According to the World Health Organization (WHO), there were an estimated 480 000 new cases of multidrug-resistant TB in 2015 (2). Drug resistance surveillance data show that 3.9% of new and 21% of previously treated TB cases were estimated to have had rifampicin-or multidrug-resistant tuberculosis. The incidence of MDR-TB was 4.4% among new cases in 2015 in Kenya (3). Drugs used for MDR-TB treatment, are grouped into 5 categories according to efficacy, the experience of use and drug class as shown in table 1. Treatment mainly involves the use of drugs from group 1-4.

Table 1. Drugs used in the treatment of MDR-TB

Group	Drug
1	Pyrazinamide, Ethambutol, Rifabutin, and Isoniazid
2	Aminoglycosides – Kanamycin or Amikacin, Capreomycin
3	Fluoroquinolones-Levofloxacin, Moxifloxacin
4	Ethionamide (or protionamide), cycloserine Terizidone
5	Clofazimine, Linezolid, Amoxicillin/clavulanate, Thiacetazone, Imipenem/cilastatin, high-dose isoniazid, and Clarithromycin

Occasionally depending on the response, group 5 agents can be added. Group 1 drugs are the most potent and best tolerated. Group 2 which consists of aminoglycosides is the first choice of an injectable agent. Patients who cannot tolerate aminoglycosides are given capreomycin. All

patients receive a group 3 medication and a group 4 agents because of their effectiveness and low cost. When two agents are needed, cycloserine can be added.

Terizidone can be used instead of cycloserine and is assumed to be equally efficacious. In Kenya, MDR-TB treatment is accomplished in two phases (4). The intensive phase and continuation phase lasts for 8 and 12 months respectively. Five drugs are used during the intensive phase and these are; Kanamycin or capreomycin, Protionamide, levofloxacin, cycloserine, and pyrazinamide. Drugs used in the continuation phase are; levofloxacin, protionamide, cycloserine, and pyrazinamide. Extensively drug-resistant tuberculosis (X-MDR- TB) is treated for a longer period. The intensive phase takes 12 months and drugs used are; capreomycin, moxifloxacin, para-aminosalicylate, clofazamine, and amoxicillin/ clavulanate. The continuation phase lasts for 18 months and drugs used are moxifloxacin, PAS, clofazimine and amoxicillin/ clavulanate. A shorter treatment regimen is being initiated among newly diagnosed MDR-TB cases which lasts for nine months.

Although the incidence of MDR-TB cases is on the rise, no previous study has been done to assess the effects of the drugs among patients in Nairobi City County. The objective of this study was to evaluate the adverse drug events of MDR-TB therapy.

Methods

A retrospective longitudinal design was used. All the participants suffering from drug-resistant tuberculosis and attending health facilities in Nairobi City County for treatment were eligible to participate in the study. The participants were; on drug-resistant TB drugs for at least one month, aged 18 years and above, able to communicate effectively and consented to participate in the study.

Approval to carry out the study was given by Kenyatta National Hospital- University of Nairobi Ethical and Research Committee. Permission was also granted by the department of health of Nairobi City County. The managers for the respective health facilities where data were collected also gave a nod.

All the twenty-three participants who were accessible and eligible during the study period were assessed. A researcher administered questionnaire was used to collect data. The participants were individually invited for a face to face interview and responses entered into the questionnaire. This was done in a place within the health facility where only the researcher and participant were present to ensure confidentiality. These facilities were Kenyatta National Hospital and several health centers including; Dandora phase I and II, Westlands, Bahati, and Langata. Some of the data that could not be obtained directly from the participant were abstracted from the clinic records and entered into the questionnaire. This included the serum levels of potassium, creatinine, hemoglobin, liver enzymes and thyroid hormones. Hepatotoxicity was diagnosed if the serum level of alanine aminotransferase was elevated. Nephrotoxicity was detected if the serum creatinine was elevated. Low or high serum potassium levels were interpreted as hypokalemia and hyperkalemia respectively. Anemia was characterized by low level of hemoglobin.

Results

Sociodemographic characteristics

Twenty-three participants were recruited in the study and 17(73.9%) were males (Table 2). The the majority (13, 56.5%) of the respondents were married. The mean age was 37.1(SD+/- 11.4) years and the range was 20 to 50 years. Fifteen (65.2%) respondents were below forty years of age Eleven (47.8%) participants had normal body mass index but 9(39.1%) had lower than required. All the participants were literate, 6(26.1%) had a primary education while 12(52.2%) had attained the secondary level of education. Previous lifestyle habits before diagnosis and initiation of treatment of the disease were smoking and alcoholism which were associated with 10(43.5%) respondents. Eleven (47.8%) participants had previous episode of tuberculosis infection. The comorbidities present were human immuno-deficiency virus infection (10, 43.5%), malnutrition (9, 39.1%) and diabetes mellitus (1, 4.4%) respectively.

Table 2. Socio demographic characteristics (N=23)

Variable	Frequency	Percent
Sex		
Male	17	73.9
Female	6	26.1
Marital status		
Married	13	56.5
Single	10	43.5
Age category (years)		
18-30	8	34.8
31-40	7	30.4
Above 41	8	34.8
Body mass index		
Below 18.5	9	39.1
18.6-25	11	47.8
25.1-30	2	8.7
Above 30	1	4.4
Level of education		
Primary	6	26.1
Secondary	12	52.2
Tertiary	5	21.7
Comorbidities		
HIV infection	10	43.5
Malnutrition	9	39.1
Diabetes mellitus	1	4.4
Alcoholism	10	43.5
Tobacco smoking	10	43.5
Previous hospitalization	3	13.0
Previous TB infection	11	47.0

Prevalence of adverse drug events

Several drugs were used depending on the phase of therapy (Figure 1). Six (26%) respondents were in the intensive phase of treatment where five drugs were used including; kanamycin (kn) or capreomycin (Cm), levofloxacin, protionamide(PTO), cycloserine (CS), and pyrazinamide. Another six (26%) patients were on high

dose isoniazid (H), ethambutol (E), pyrazinamide (Z), kanamycin (kn), moxifloxacin (Mfx), protionamide, and clofazamine (Cfx). The continuation phase was accomplished with four drugs including; levofloxacin (Lev), protionamide, cycloserine, and pyrazinamide. (Figure Next page)

The participants experienced several adverse drug events as shown in figure 2 and table 3 respectively. Twenty-one (91.3%) participants exhibited nervous system (NS) disturbances which included; drowsiness, tingling sensation, headache, dizziness, insomnia, depression, and nightmares. Gastrointestinal tract (GIT) disturbances were the second most prevalent where 20 (87%) participants were affected and complained of nausea, vomiting, abdominal pain, flatulence,

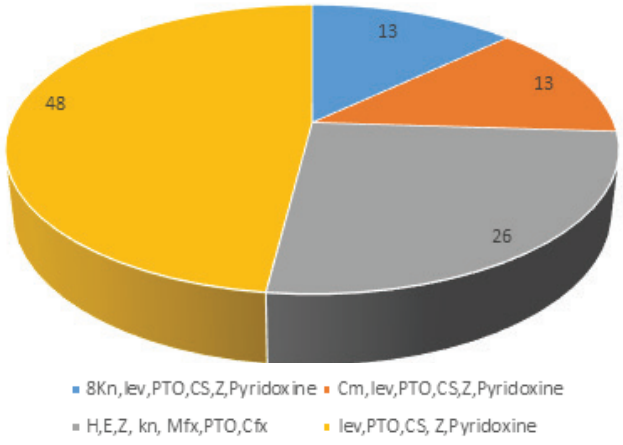

Figure 1. Types of drug regimens

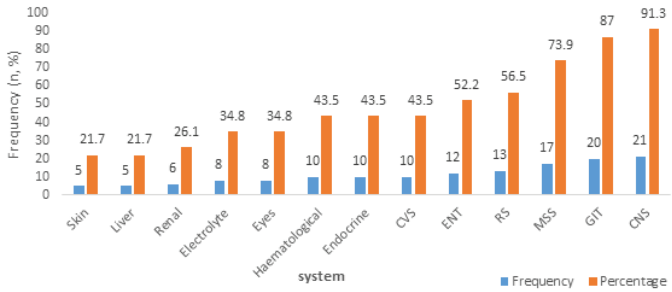

Figure 2. Systemic categorization of adverse drug events due to MDR-TB drugs.

excessive salivation, diarrhea, constipation, abdominal cramps, loss of appetite, black tarry stool, dry mouth and mouth ulcers. Seventeen (73.9%) respondents suffered from the musculoskeletal system (MSS) adverse effects including joint pains, backache, muscle spasms and pain in the big toe. Respiratory system was affected in 13(56.5%) participants who presented with a cough, chest pain and dyspnea. Twelve (52.2%) respondents had ear, nose, and throat (ENT) problems and the most common was a loss of hearing. Cardiovascular system (CVS) was affected in 10(43.5%) cases who had palpitations. Among the 10(43.5%) who had endocrine disturbances, 7(30.4%) had hypothyroidism and 5(21.7%) experienced sexual dysfunction. Eight (34.8%) participants complained of visual disturbances while 5(21.7%) and 3(13%) were victims of hyperkalemia and hypokalemia respectively. Among the 10(43.4%) participants with hematological problems,

Table 3. Prevalence of adverse drug events of MDR-TB therapy (N=23)

Adverse event	n	%	Adverse event	n	%
Nephrotoxicity	6	26.1	Mental depression	8	34.8
Hypothyroidism	7	30.4	Agitation	6	26.1
Hyperkalemia	5	21.7	Cough	6	26.1
Hypokalemia	3	13	Chest pain	5	21.7
Anemia	9	39.1	Dyspnea	4	17.4
Hepatotoxicity	6	26.1	Painful urination	3	13
Nausea	20	87	Frequent urination	5	21.7
Vomiting	15	65.2	Reduced urine	3	13
Abdominal pain	12	52.2	Joint pains	15	65.2
Flatulence	17	73.9	Backache	9	39.1
Excessive salivation	15	65.2	Pain in the big toe	3	13
Diarrhea	1	4.4	Muscle spasms	3	13
Constipation	3	13	Fullness in the ears	2	8.7
Abdominal cramps	12	52.2	Deafness	10	43.5
Loss of appetite	11	47.8	Vertigo	1	4.4
Black tarry stool	2	8.7	Sore throat	1	4.4
Dry mouth	5	21.7	Sexual dysfunction	5	21.7
Mouth ulcers	1	4.4	Bleeding	2	8.7
Palpitations	7	30.4	Malaise	14	60.9
Headache	9	39.1	Jaundice	1	4.4
Dizziness	9	39.1	Visual impairment	7	30.4
Confusion	4	17.4	Weight gain	3	13
Irritability	8	34.8	Fever	1	4.4
Nightmares	6	26.1	Paleness of the skin	1	4.4
Drowsiness	11	47.8	Tremor	2	8.7
Speech problems	2	8.7	Rash	5	21.7
Suicide thoughts	5	21.7			
Tingling sensation	10	43.4			
Insomnia	9	39.1			

anemia was the most common. The other less common but serious adverse drug events were nephrotoxicity (6, 21.6%), hepatotoxicity (5, 21.7%) and rash (5, 21.6%). All the participants suffered from many adverse events and 12(52.2%) experienced ten and below while 11(47.8%) had more than ten.

Bivariate analysis of adverse drug events and MDR-TB regimens

A bivariate analysis was conducted using Fischer's exact test between the type of MDR-TB regimen used and adverse drug events and the results are shown in table 4.

Table 4. Association between adverse drug events and MDR-TB regimens (N=23)

System/Organ	Type of regimen				P value
	R1 (n, %)	R2 (n, %)	R3 (n, %)	R4 (n, %)	
Renal	0	2(8.7)	4(17.4)	0	0.097
Endocrine	0	1(4.3)	7 (30.4)	2(8.7)	0.267
Electrolyte	0	2 (8.7)	3 (13)	3 (13)	0.408
GIT	3 (13)	3 (13)	8 (34.8)	6 (26.1)	0.590
CVS	1(4.3)	1(4.3)	6 (26.1)	2(8.7)	0.927
CNS	3 (13)	3 (13)	10 (43.5)	5 (21.7)	1
RS	2 (8.7)	2 (8.7)	5 (21.7)	5 (21.7)	0.927
MSS	2 (8.7)	3 (13)	8 (34.8)	4 (17.4)	0.912
ENT	2 (8.7)	2 (8.7)	7 (30.4)	1(4.3)	0.261
Eyes	1(4.3)	1(4.3)	6 (26.1)	0	0.138
Skin	1(4.3)	0	1(4.3)	3 (13)	0.217
Haematological	0	1(4.3)	4 (17.4)	2(8.7)	0.836
Liver	0	0	4 (17.4)	1(4.3)	0.515

R1-8kn, lev, PTO, CS, Z, Pyridoxine R2- Cm, lev, PTO, CS, Z, Pyridoxine

R3- lev, PTO, CS, Z, Pyridoxine R4- H, E, Z, Kn, Mfx, PTO, Cfx

Generally, more adverse events were experienced by the participants who were using the R3 and R4. Despite this observation, there was no statistical relationship between the type of MDR-TB regimen used and adverse events that were experienced by the participants.

Bivariate analysis of adverse drug events and phase of MDR-TB therapy

Additional analysis was done using Fischer's exact test between the phase of therapy and adverse drug events and the results are shown in table 5.

Table 5. Association between adverse drug events and phase of therapy (N=23)

System/ Organ affected	Phase of therapy		P value
	Intensive phase (n, %)	Continuation phase (n, %)	
Kidney	3 (13)	3 (13)	1
Endocrine	2 (8.7)	8 (34.8)	**0.012***
Electrolytes	4 (17.4)	4 (17.4)	1
Gastrointestinal tract	12 (52.2)	8 (34.8)	0.093
Cardiovascular	4 (17.4)	6 (26.1)	0.414
Nervous	11 (47.8)	10 (43.5)	1
Respiratory	8 (34.8)	5 (21.7)	0.414
Musculoskeletal	9 (39.1)	8 (34.8)	1
Ear	5 (21.7)	7 (30.4)	0.414
Eyes	2 (8.7)	6 (26.1)	0.089
Skin	4 (17.4)	1 (4.3)	0.317
Blood	4 (17.4)	3 (13)	1
Liver	1 (4.3)	4 (17.4)	0.155

****- Statistically significant p-value***

Endocrine disturbances were more common in the continuation phase than an intensive phase and the difference was statistically significant (p=0.012). The other adverse drug events were present in both phases and the differences in their occurrence were not statistically significant between the two phases.

Discussion

Male predominance was observed in the study which has been observed elsewhere (5). Both genetic and behavioral characteristics are predisposition factors. Males are known to be more outgoing than women and androgens are known to suppress the immune system of the body. About a third of the participants were undernourished which was lower than that from an Indian study (5). Tuberculosis is a catabolic disease and also cause anorexia leading to loss of body mass. HIV coinfection had a prevalence of 43.5% which was quite high. The disease destroys the body immune system especially the cell-mediated one which protects the body against intracellular microorganisms. Tobacco smoking and alcoholism are also known to be immunosuppressant in different ways. Forty-seven percent of the respondents had relapsed tuberculosis suggesting that the resistance was acquired against first-line drugs due to different reasons such as non-adherence or poor quality drugs.

The most common side effects were central nervous disturbances (91.3%) which were most likely due to cycloserine, isoniazid, levofloxacin, and moxifloxacin. The prevalence of these adverse drug events was higher than what was noted in a study from South Korea (6). The most common symptoms were drowsiness, depression, and insomnia which were more prevalent than what was found in an Ethiopian study (7). Peripheral neuropathy which presented as tingling and burning sensations in the extremities was mainly due to isoniazid, ethambutol, and prothionamide. Isoniazid is a competitive inhibitor of pyridoxine in the nerves. Gastrointestinal disturbances such as nausea, vomiting, and abdominal pain had a prevalence of 87% which was higher than a similar study done in Namibia (8) and drugs that were are implicated included prothionamide, quinolones, isoniazid, and pyrazinamide. Musculoskeletal side effects such as muscle spasms, backache, and joint pains were probably due to the accumulation of uric acid triggered by pyrazinamide which reduces its excretion. Ototoxicity manifesting as hearing loss, dizziness and vertigo were due to Kanamycin and capreomycin which damages the auditory nerve and the prevalence was higher than from a Korean study (6). Visual impairment was reported by 30.4% of the respondents which was higher than that from an Ethiopian study (8). Ethambutol was probably the culprit since it damages the optic nerve. Hepatotoxicity occurred in 26.1% of the respondents which was higher than that from a Korean study (6) and drugs responsible were protionamide, isoniazid, and pyrazinamide which are known to damage the hepatocytes. Nephrotoxicity occurred in 26.1% of the respondents which was higher than that observed in Ethiopia (8) and the drugs responsible were kanamycin and capreomycin. The damage to the kidneys was the main cause of hyperkalemia, hypokalemia, and changes in the frequency of urination. Anemia that occurred in 39.1% of the cases and was likely due poor feeding habits and

myelosuppression which usually occurs in chronic illnesses.

Conclusion

Drug-resistant tuberculosis was more common in males than females. Many participants suffered from the adverse events of drugs which became less severe as the treatment progressed from intensive to the continuous phase. These adverse events manifested in all body systems with the nervous and gastrointestinal tract being most affected.

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