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FEATURE ARTICLE:

The effect of processed *Camellia sinensis* on acute amitraz poisoning in a rat model

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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

PHARMACEUTICAL CARE OF A CRITICALLY ILL PATIENT

Prof. Apollo O. Maima, PhD, MPSK
Editor-in-Chief and Chair of the Editorial Board, Pharmaceutical Journal of Kenya

Introduction

Pharmaceutical care of critically ill patients is complex due to morbidity, organ failures, and comorbidities [1]. Pharmacotherapy must be tailored to each patient's unique scenario, considering systemic disorders, pharmacokinetics, and non-pharmacological interventions. Elderly patients with age-related drug metabolism changes require urgent solutions [2]. An all-encompassing approach with blood sampling, pharmacokinetic simulation, and non-pharmacological interventions can optimize treatment. The goal is to tailor pharmacotherapy to each patient, reducing toxic side effects and maximizing response. The approach depends on the patient's multidimensional situation and the critical care unit environment. Nevertheless, efforts should focus on safely, reinforcing therapeutic signals and decreasing polypharmacotherapy dynamics [3].

Importance of Pharmaceutical Care in Critical Illness

Prolonged critical illness is challenging to treat and can lead to disability; anemia, thrombosis, sepsis, and bleeding are common complications. Effective pharmaceutical care interventions improve patient outcomes while vigilant monitoring is crucial [4]. Active pharmaceutical care involves individual medication dosing and surveillance of drug effects, both of which can achieve prevention of complications and reduction of length of hospital stay [5]. Pharmacists play a vital role in identifying and resolving drug problems; and contribute to the healthcare team's care plan [6, 7].

Pharmacokinetics and Pharmacodynamics in Critically Ill Patients

Critically ill patients can have altered pharmacokinetics and pharmacodynamics, leading to especially changes in drug absorption, distribution, metabolism, and excretion. This can result in sub-therapeutic doses that may need to be increased for desired drug concentrations; or toxic levels due to lowered drug metabolism and clearance [8]. Inter-organ dysfunction can also impact drug biotransformation and organ volume. Pharmacodynamic changes can cause variations in drug action, particularly for drugs with narrow therapeutic indices. It is therefore important for healthcare providers to closely monitor drug levels and adjust dosages accordingly in critically ill patients. Guidelines are available for accounting for these variations and managing potential adverse outcomes. Specific subgroups, such as pregnant women; and hemodialysis, oncology and cystic fibrosis patients, have dedicated publications on appropriate drug dosing. However, it is note-worthy that automatic clinical decision-making based solely on therapeutic drug monitoring may not consider other factors such as desired therapeutic outcomes and potential interactions [9].

Drug Interactions and Adverse Effects in Critical Care Settings

Drugs given in critical care carry risks of interactions hence pharmacotherapy for critically ill patients must rely on measurable beneficial indices of drugs or dose schedules. Anticipating occurrences of limited interactions is vital. Complexity increases with patient, disease, pharmacological, and drug formulation factors, contributing to the risk of polypharmacy [10]. Consequences of interactions range from minor effects to enhanced efficacy or toxicity, therapeutic failure, or sudden death. Adverse effects have low incidence and unpredictable relation to side effects in a small number of patients, making interpretation of placebo studies and assessment of new drug therapy difficult. Genetic predisposition can lead to adverse reactions to standard doses. High-risk intravenous drugs in standard dilutions pose a rare but serious threat [11].

Pharmaceutical Care Strategies in the Intensive Care Unit

Pharmaceutical care improves patient's quality of life through responsible provision of drug therapy. Comprehensive medication management is crucial, involving problem identification and optimal drug therapy regimen design. A systematic approach is essential, with assessment and data gathering by a healthcare team. Interventions are summarized, documented, and undertaken by individual healthcare providers. In the ICU, medication reviews and clinical pathway programs aid pharmaceutical care. Pharmacists participate in daily rounds and emphasize patient education. Inpatient surveillance of adverse drug reactions and strict monitoring policies are key [12].

Conclusion

Pharmaceutical care ensures safe and effective medication use in critically ill patients. The ICU pharmacist plays a crucial role in medication delivery and outcomes. Individual

treatment plans and changing parameters influence the care process. Ongoing education is necessary to improve pharmaceutical care in ICUs. Integrated care and ongoing research are important for the future. Inter-professional training and cooperation are essential for better patient care.

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Prevalence and determinants of drug-related problems among patients in the critical care unit of Kenyatta National Hospital

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Abstract

Background: Critically ill patients tend to be at risk of drug-related problems due to several factors, such as their state of illness, polypharmacy, and inability to participate in their care. This study aimed to characterize drug-related problems (DRPs) and their determinants among patients admitted to the intensive care unit (ICU) of Kenyatta National Hospital (KNH).

Methods: A cross-sectional design study was conducted at the three critical care units of KNH and 87 participants were involved. Simple random sampling was used to select participants and data were abstracted from the patient records using a predesigned data collection tool. The data were entered into Microsoft Excel 2010 and analyzed using STATA version 13.0 using both descriptive and inferential statistics at 0.05 level of significance.

Results: The prevalence of DRPs among patients admitted to the ICU of KNH was 59.77%. High dosage (5.75%), adverse reactions (6.9%), need for additional drug therapy (16.1%), drug interactions (19.54%) and noncompliance (26.44%) were the major categories of DRPs. Polypharmacy (p=0.001), multiple prescribers (p=0.01), and renal impairment (p=0.004) were the independent predictors of DRPs.

Conclusion: The prevalence of DRPs was high. The significant determinants of DRPs were polypharmacy, multiple prescribers, and renal disorders.

Key words: *Drug-related problems, intensive care units, Kenyatta National Hospital.*

Introduction

A drug therapy problem is any undesirable event experienced by a patient that involves or is suspected to involve drug therapy which interferes with the desired therapeutic goals and requires professional judgment to resolve the occurrence of DRPs. DRPs result from a patient's drug-related needs that have not been fully met, and these form the basis for pharmaceutical care practice [1]. DRPs can be considered a clinical problem that needs to be identified, treated, or prevented. According to Hepler and Strand, there are eight categories of drug-related problems namely: untreated indications, improper drug selection, sub-therapeutic dosage, failure to receive drugs, overdose, adverse drug reactions, drug interactions, and drug use without indication [2,3]. The treatment of critically ill patients involves several drugs that have the potential to cause serious harm [4,5].

Polypharmacy is a risk factor for drug-related problems since it increases the occurrence of drug-drug interactions [4,5]. Due to their state of illness, these patients tend to require dose adjustments, which require calculations that may result in arithmetic errors [6]. The complexity of their treatment, coupled with their state of health and inability to participate in their treatment among the majority of these patients means that they are more vulnerable to DRPs than the average patient. Critically ill patients receive twice the number of medications that non-critically ill, hospitalized patients receive, thus increasing the prevalence of adverse drug events.. ICU patients are more likely to have drug-drug interactions, drug accumulation due to failing organs, and a sensitivity to drug responses resulting from their labile status. The complexity of the patient's treatment plans and the environment provide a risk for patient harm.

Critically ill patients are also more likely to develop drug-induced events such as acute kidney injury and coagulopathies. Even though healthcare professionals are very concerned about patient safety, mistakes or errors unavoidably occur especially in a complex setting like the ICU [6]. A study carried out in Saudi Arabia found that 3.6% of all admissions in the ICU were due to DRPs [7]. In 2015, a similar study conducted in Brazil found a drug-related problem prevalence of 97.4% (8). From the literature review, it was evident that there is a paucity of data on the extent of drug-related problems among critically ill patients receiving care in intensive care settings. The paucity of such data was

more for resource-limited settings such as Kenya and other Sub-Saharan African settings. Given the complexity of treating critically ill patients and the many risk factors they have, they are more susceptible to drug-related problems. Hence, this study aimed to assess the prevalence and determinants of DRPs in patients admitted to the intensive care unit of Kenyatta National Hospital.

Methodology

Study design, setting, and period

This study used a cross-sectional design and was carried out for two months. It involved a direct observation of patients admitted in the critical care units of KNH and a review of the medical records and medication charts, to check for real or potential DRPs at the point of contact. The study site was Kenyatta National Hospital, a teaching and referral hospital based in Nairobi, Kenya. It is currently the largest national referral, teaching, and research hospital in the country. It also provides facilities for medical education for the University of Nairobi (UON) and Kenya Medical Training College (KMTC) and conducts research either directly or through other collaborating health institutions. The hospital has a critical care unit spread across three wards.

Study population

The study participants were patients admitted in the critical care units which admit 56 patients on average monthly.

Eligibility criteria

Inclusion criteria

All patients admitted in the ICU who were on drug therapy.

Exclusion criteria

Any patients admitted to the ICU who died within 24 hours of admission.

Sample size and sampling method

The sample size was determined using the Fischer formula (9). Since no local studies have been carried out, the prevalence was assumed to be 50%. Since the source population was less than 10,000 a reduction formula was also applied to estimate the final sample size. Hence, a total of 87 study participants were recruited. Simple random sampling was used to select the participants.

Research instruments

A well-structured and validated tool was used to extract data from patient records. Patient socio-demographic characteristics were retrieved from the inpatient patient files. The tool had two sections. Section one was used to capture the socio-demographic and clinical characteristics and section two had details relating to the occurrence of DRPs and associated risk factors.

Pre-testing of the data collection tool

This was done using ten participants and the instrument was revised to enhance its validity and reliability.

Validity of the study

External validity was assured by having an adequate sample size and internal validity was achieved by having appropriate questions to capture both the independent and dependent variables.

Data collection techniques

Data were collected for one month. At the point of contact, the patient demographics were captured, as well as the patient history, the treatment regimen, and any notable risk factor of DRP as well as any DRP present. This data was collected from the inpatient files, treatment sheets, laboratory reports, and any other relevant diagnostic tests.

Data analysis

The data were entered into Microsoft Excel and analyzed using Stata version 13.0 software. The results were presented using mean, frequency tables and figures. Binary logistic regression analysis was carried out to investigate the predictors of DRPs. The associations between variables were deemed significant where the p-value was less than or equal to 0.05.

Ethical approval

Ethical approval was obtained from the University of Nairobi and Kenyatta National Hospital-Ethics and Research Committee (KNH/UON-ERC) before carrying out the study (Approval No: KNH-ERC/A/443. The authorization to conduct the study was obtained from the KNH administration. Participation in the study was voluntary and was done after the participants consented.

Results

Socio-demographic and clinical characteristics

The majority of the participants 55, (63.2%) were males and 39(47.6%) were 15-45 years of age. It was also established that 43 (49.4%) participants were married and 40 (45.9%) were unemployed. Eight (9.20%) and 14 (16.1%) participants had a history of smoking and drinking alcohol, respectively **(Table 1)**.

Table 1. Socio-demographic characteristics (n=87)

Variable	Frequency (%)
Gender	
Males	55(63.2)
Females	32(36.9)
Age	
0-14years	11 (13.4)
15-45 years	39 (47.6)
46-65years	25 (30.5)
>65 years	7 (8.5)
Not Indicated	5 (5.8)
Marital status	
Married	43(49.4)
Single	28(32.2)
Not Indicated	16(18.4)

Education level	
None Primary Secondary Tertiary Not Indicated	10(11.5) 13(14.9) 23(26.4) 9(10.3) 32(36.8)
Occupation	
Unemployed Employed Not indicated	40(45.9) 22(25.3) 25(28.7)
Smoking	
Yes No Not indicated	8 (9.2) 46(52.9) 33(37.9)
Alcohol	
Yes No Not indicated	14(16.1) 41(47.1) 32(36.8)

Prevalence of drug-related problems

Most participants (65, 74.71%) were on antimicrobial drugs. The other medications used were mainly anticonvulsants (48, 55.17%), and analgesics (37, 42.53%). Fifty-two (59.78%) participants experienced drug-related problems. Noncompliance (23, 26.4%) was the most common followed by drug interactions (17, 19.5%) and the need for additional drug therapy (14, 16.1%) as shown in **Figure 1**.

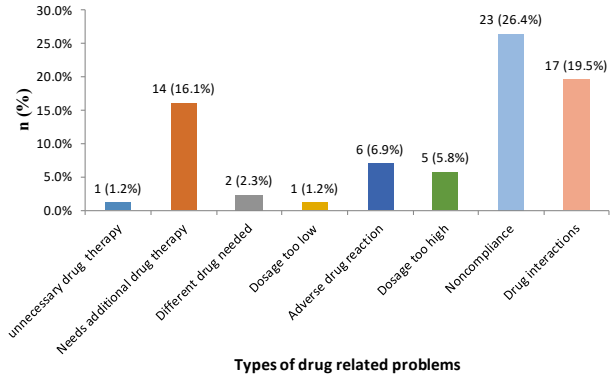

Figure 1. Prevalence of drug related problems

Predictors of drug related problems

The results showed that patients who had polypharmacy were 13.26 times more likely to have DRPs (AOR=13.26, 95% CI=1.49-118.25, p=0.021) compared to those who did not. In addition, patients who were attended by many prescribers were 13.51 times more likely to experience DRPs. Patients who had renal impairment (AOR=0.019, 95% CI: 0.001-2.75, p=0.004) were probably 0.019 times more likely to experience DRPs (**Table 2**)

Table 2. Predictors of drug related problems.

Frequen	Bivariable analysis		Multivariable analysis	
	COR (CI)	P-value	AOR (CI)	P-value
Female	2.83 (1.17, 6.87)	0.021*	2.81 (0.74, 10.7)	0.129
Benzodiazepines	2.67 (0.87, 8.13)	0.085	0.88 (0.18, 4.42)	0.879
Antimicrobials	3.67 (1.33,10.1)	0.012*	4.48 (0.97, 20.62)	0.054
Polypharmacy	8.18 (2.74, 24.46)	0.001*	13.26(1.49, 118.25)	0.021*
Multiple prescribers	4.46(1.37, 14.49)	0.013*	13.51 (1.65,110.71)	0.015*
Medicine specific factors	8.10 (0.99, 66.42	0.051	114.54 (3, 4359.02)	0.11
Renal impairment	0.36 (0.11, 1.21)	0.098	0.019 (0.001,2.75)	0.004*

COR: Crude odds ratio, AOR: Adjusted odds ratio, CI: Confidence interval, *:-statistically significant p-value

Discussion

The study assessed the prevalence and types of drug-related problems and their determinants in the critical care unit of a Kenyan tertiary health facility. Globally, DRP remains one of the public health problems, and about 10%–20% of inpatients will have at least one adverse drug reaction during their hospital stay (10). Patients admitted to critical care can often experience both rapidly changing organ dysfunctions and multiple transitions of care. The prevalence of DRP in this study was high and this observation concurs with a study done in Thailand (11). The most common drug therapy problems observed were high dosage, adverse reactions, need for additional drug therapy, drug interactions, and noncompliance. A similar study shows that the most common types were dosage too high, ineffective drug, need for additional drug therapy, unnecessary drug therapy, dosage too low, adverse drug reaction, and non-adherence (11). The patients in the critical care unit often use many drugs concurrently due to the complexities of their illness leading to profound changes in the body. Therefore drug-drug and drug-disease interactions are bound to occur. A study carried out in Nepal showed a high prevalence of DRPs among patients in the critical care unit and the association between dose selection and gender was significant (12). Drug selection issues were more observed in patients using multiple drugs and with a shorter hospital stay (12).

Polypharmacy, multiple prescribers, and renal impairment were the significant predictors of DRPs. An Ethiopian study reported that polypharmacy, prolonged hospital stay, and co-morbidities were independent predictors of DRPs (13,14). Polypharmacy may lead to poor adherence, drug interactions, and adverse drug events. The use of multiple medications has been shown to increase admissions to the hospital and mortality (15). The treatment of renal complications requires numerous medications. The manifestations of other medical disorders in patients during renal treatment attract the use of other medications resulting in drug therapy problems. A study in Nigeria found that drug therapy problems among renal patients were high (16). Nonetheless, patients who had renal impairment were less likely to experience DRPs in this study setting. This could be probably because of the extra care the prescribers observed among patients with renal impairment.

Conclusion

The prevalence of DRPs was high and the most prevalent ones were non-compliance to medicines, drug interactions, and the need for additional drug therapy. Polypharmacy, multiple prescribers, and renal impairment were independent predictors of DRPs.

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Evaluation of Oxytocic Activities of Methanol Extract and Aqueous Fraction of *Opuntia ficus-indica* (L.) Mill. (Cactaceae) Stem in Rats *In vitro*

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Abstract

The research evaluated the in vitro oxytocic potential of crude methanol (MeOH) extract and aqueous (AQ) fraction of *Opuntia ficus-indica* stem in non-pregnant female rat. Spontaneous contraction, oxytocin pretreated uterus in both normal physiological salt solution and calcium ions free medium, as well as high potassium chloride (KCL) concentration-induced models were used. MeOH extract was more potent than AQ fraction when tested at 0.2 - 2.0 mg/mL in stimulating concentration-dependent increase (up to 0.8 mg/mL) in amplitude of spontaneous uterine contraction accompanied by inhibition of contraction frequency in normal salt medium. Whereas the MeOH extract gave potentiation effect only on amplitude (15.68% increase) in the oxytocin-pre-contracted experiment at the maximal concentration, AQ fraction was inactive. Both tested agents failed to potentiate oxytocin in the absence of calcium, and also inhibited high KCL by suppressing contraction amplitude. This study therefore supports the traditional use of *O. ficus-indica* stem as a labour-inducer in maternal health.

Key Words: *Opuntia ficus-indica, stem, oxytocic activity, rat uterus, in vitro.*

Introduction

Prickly pear, *Opuntia ficus-indica* (L.) Mill. (Cactaceae), originated from Mexico but is now widely distributed in the Americas, Africa and the Mediterranean [1, 2]. The fruit, a sweet flavory fleshy berry with thick peel and many seeds, has excellent nutritional properties and is rich in bioactive compounds, such as betalains, phenolics and vitamins which have been reported to possess antioxidant, anticancer, anti-inflammatory, antidiabetic, neuroprotective and antiproliferative activities, among others [2, 3]. Cactus stem and fruits are important ingredients of value-added products like jam, wine, body lotions and shampoo [2]. Prickly pear is valued in Mexican traditional folk medicine for the treatment of oedema, diabetes, indigestion, burns and wounds. The seed oil is reported to be effective in treating gastric ulcer [4]. It is also believed to play a role in facilitating childbirth in African traditional medicine (personal communication). Apart from the global review of ethnobotanical surveys of uterotonic plants in Africa [5], literature also documents labour-inducing plants in Sub-Saharan Africa [6] including Nigeria [7-10]. Recently, uterotonic effect of Psidium guajava was published by Gbolade et al. [11]. Nevertheless, no report is available on the oxytocic potential of *O. ficus-indica*.

Consequently, as part of ongoing research endeavours to document scientifically-investigated oxytocic plants in Nigeria, this study investigated methanol extract and aqueous fraction of the stem of *O. ficus-indica* for uterotonic effect in non-pregnant oestrogenized female rats.

Methodology

Plant collection and extraction

Stem of *O. ficus-indica* was harvested from Okada, Edo State, Nigeria in January 2017, and authenticated (voucher no. IUO/17/176) at Department of Pharmacognoy, Igbinedion University Okada (IUO) herbarium. The plant was cut into small pieces and air-dried for seven days on concrete floor, ground into coarse powder using a locally fabricated grinder. Powdered plant (500g) was exhaustively extracted in the Soxhlet apparatus with methanol (MeOH), filtered, and extract concentrated on an electric water bath (40^{o}C) to yield dried residue. Part of the residue was re-dissolved in water and successively partitioned exhaustively with chloroform ($CHCL_3$), ethylacetate (EtOAc) in a separating funnel to yield $CHCL_3$, EtOAc and aqueous (AQ) fractions. Fractions were concentrated to dryness and respective yields recorded. Dried extract and fractions were refrigerated (4^{o}C) until needed.

Phytochemical screening

Basic phytochemical screening was carried out on the crude methanol extract of the plant according to Sengar et al. [12] and the presence of secondary metabolites recorded.

Drugs and reagents

Stilboesterol and oxytocin (Sigma-Aldrich, USA); methanol, NaCl, $NaClO_3$, KCL, $CaCl_2$, $MgCl_2$, $NaHCO_3$ and D-glucose (BDH Chemicals, England).

Preparation of physiological salt solution

The biological assay was carried out in Pharmacology laboratory, University of Benin, Edo State, Nigeria. Firstly, the

physiological salt solution (PSS) was prepared according to Bafor *et al*. [9] by dissolving appropriate amounts of NaCl, $NaClO_3$, D-glucose and KCL in distilled water in a calibrated beaker. $CaCl_2$ was dissolved in water separately to avoid cloudiness, and then added to the initial four-salt mixture to form the PSS with final composition in mM/L: NaCl 154.00, $NaHCO_3$ 5.95, D-glucose 2.78, KCl 5.63, and CaCl2·2H2O 2.05.

Experimental animals

Healthy non-pregnant albino rats (150–180g) were utilized for this study. They were housed under standard conditions (27±5°C and natural light and dark cycles) in the Central Animal House, University of Benin, and fed with standard animal pellets (Bendel Foods and Flower Meal, Edo State, Nigeria) and water *ad libitum*. Animals were handled in accordance with the Public Health Service policy on humane care and use of Laboratory Animals [13]. Ethical permission (IUO/ETHICS/024) was obtained before the start of the experiments from the Animal Ethics Committee, College of Pharmacy, IUO, Nigeria.

Preparation of uterine tissue

Female rats previously primed with stilboesterol (1 mg/kg) for 24 h were used for the study as described by Bafor et al [9]. Animals were humanely killed by cervical dislocation and the uterine horns were immediately removed and placed in a petri dish containing previously warmed and aerated PSS. Connective and adhering tissues were removed from the isolated uterus and one horn was dissected in half to obtain a segment of the uterine horn of approximately 1–2 mm in length. Oestrogenized uterine segment obtained was mounted in a warmed tissue organ bath (10 mL) maintained at 37°C and containing aerated PSS. Organ bath was connected to an isometric force transducer (7003E- Ugo Basile, Varise, Italy) linked to a 17400 data capsule digital recorder with an inbuilt bridge amplifier (Ugo Basile, Varese, Italy). The tissue was equilibrated under resting tensions of 4.90 mN for 30–45 min or till regular contractions were obtained.

Determination of uterine contractility

MeOH extract (0.001–0.647 mg/mL) was added cumulatively to the organ bath containing isolated oestrogenized uterine tissue suspended in PSS to obtain concentration-response relationships according to Bafor *et al.* [9] Concentrations used were previously determined in our laboratory constituting the total effect of the extract. Each concentration was allowed a contact time of 5 min before measuring the amplitude and frequency of contraction. Effect of extract and fractions on oxytocin-induced uterine contraction was similarly determined by adding cumulative concentrations of tested samples (0.001–0.647 mg/mL) to the tissue pre-contracted with 6.7 µg/mL oxytocin. Furthermore, samples (10 mg/mL) were tested on isolated uterus pre-contracted with high KCL concentration (80 mM/mL).

Determination of effect of extract in Ca2+-free medium

In this experiment performed according to Bafor *et al.*, [9], PSS devoid of calcium was used, and ethylene diamine tetra-acetic acid (EDTA) was substituted. Oestrogenized uterine tissue was initially equilibrated for 30 min with former PSS and replaced with EDTA (1mM). Tissue was then equilibrated in this Ca2+-free solution for 3–5 min (it was essential that contractions were not totally diminished during the experiment to allow for measurements). After equilibration, oxytocin (6.7 µg/mL) was added and a contact time of 5 min was allowed. Without flushing, extract or fraction (10 mg/mL) was added. A contact time of 5 min was allowed for each sample before measuring amplitude and frequency of contraction.

Results and Discussion

Saponins, flavonoids, alkaloids, steroids, phenolic compounds and terpenoids were detected in the stem bark methanol extract of plant (Table 1). From (Panel A: Figures 1C) addition of crude MeOH extract (0.2 - 2.0 mg/mL) to uterine tussue suspended in normal PSS resulted in concentration-dependent increase in amplitude of spontaneous contraction from 0.408 gr at the least concentration to 0.881 gr (115.97%) at a four-fold concentration of extract. This was accompanied by a slight decline (36.32%) in amplitude to 0.849 gr at the highest concentration (2.0 mg/mL). However, extract produced concentration-dependent decrease in contraction frequency which was maximal at 0.8 mg/mL. Occurrence of maximal increase in amplitude and maximal reduction in frequency by *O. ficus-indica* extract at 0.8 mg/mL is noteworthy. A similar trend was recorded in amplitude (23.16 - 62.40% increase) with AQ fraction tested at similar concentrations (Panel A: Figure 1C). Conversely, both extract and AQ fraction inhibited frequency of contraction, but a sudden elevation (33 peaks/min, 94.11% increase) was observed with AQ fraction at the highest concentration (2.0 mg/mL) (Panel A: Figure 1D). In considering both parameters, the crude extract which manifested twice the amplitude potency of AQ fraction at lower concentrations, is a more active natural product contractile agent.

Table 1. Phytochemical screening of crude methanol extract of *Opuntia ficus-indica* stem.

Class of Phytochemical	Result
Alkaloids	+
Cardiac glycosides	-
Flavonoids	+
Terpenoids	+
Tannins	-
Steroids	+
Saponins	+
Phenolic compounds	+

Key: Present (+), Absent (-)

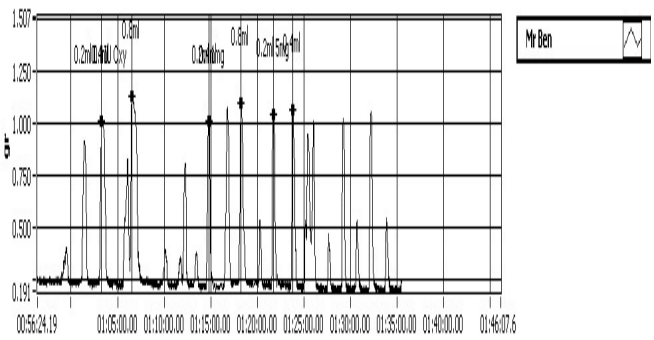

Figure 1A. Chart recording of Opuntia ficus-indica (OFI) crude extract on uterine contraction contractions on spontaneous contraction of non-pregnant uterus

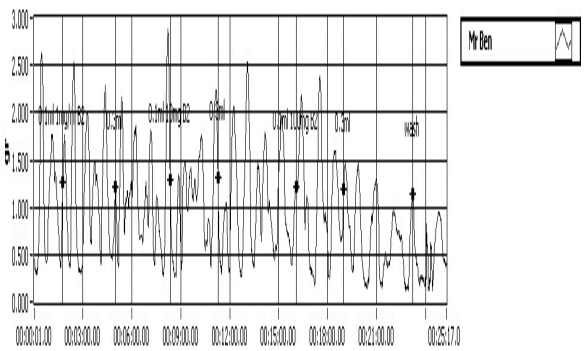

Figure 1B. Chart recording of aqueous (AQ) fraction of OFI on spontaneous uterine contraction.

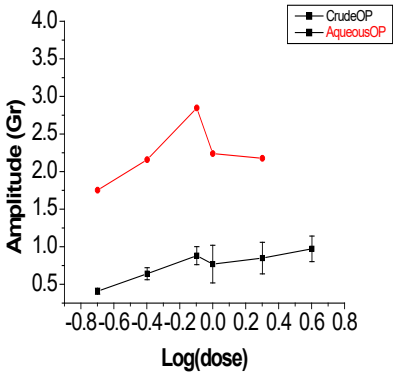

Figure 1C. Effect of OFI on amplitude of spontaneous contraction of non-pregnant rat uterus

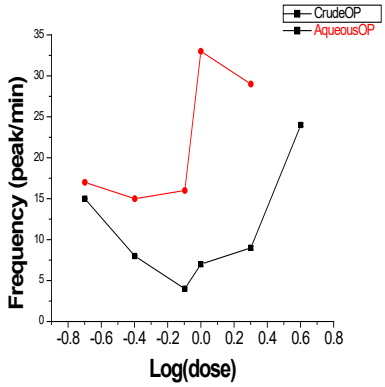

Figure 1D. Effect of OFI on frequency of spontaneous contraction of non-pregnant rat uterus

PANEL A. Effect of *Opuntia ficus-indica* on spontaneous contraction of non-pregnant rat uterus

Ability of *O. ficus-indica* extract to elicit oxytocin-like action on non-pregnant uterus is a pointer to similar mecahnism of action with this agonist. Mechanism of uterine contractility of oxytocin is reported to be via myometrial oxytocin receptors and on endometrial oxytocin receptors to stimulate prostaglandins and cholinergic releases [14], as well as by elevating intracellular calcium concentration [5, 15, and 16]. Some bioactive oxytocic coumpounds have been isolated from certain plants including *Ficus exasperata* that furnished flavonoid and pheophobide derivatives [8] which have been linked with inhibition of frequency of uterine contraction in a spontaneous contraction model. These authors also reported a pyrimidine derivative as a stimulant of spontaneous contractions. This study suggests ability of MeOH extract and AQ fraction to activate the pathways involved in stimulation of uterine contraction. Results of this investigation are also in agreement with the reports of Watcho *et al*. [14] on *Ficus asperifolia* fruit, Gbolade et al. [15] on *Psidium guajava* stembark, Bafor et al. [8] on Ficus exasperata leaf, Bafor et al. [9] on *Justica flava* leaf and Chanda et al. [17] on *Azanza garckeana* root.

In the oxytocin-pre-contracted (6.7 µg/mL) tissue experiment, only the extract, tested at maximal concentration, 2 mg/mL, potentiated oxytocin through 15.68% increase in amplitude, and with a sharp decline (45.75%) in contraction frequency (Panel B: Figures 2A-C). On the contrary, the AQ fraction inhibited both amplitude and frequency parameters. Combining Panel A and Panel B, crude extract unequivocally displayed contractile effect on non-pregnant rat tissue, being six times more effective in spontaneous contraction model (100.08% increase amplitude) than oxytocin pre-contracted experiment (15.86% increase in amplitude). Behaviour of *O. ficus-indica* MeOH extract in potentiating oxytocin is similar to the reports for other plant extracts [5,7,9]. The mechanism of potentiation of oxytocin by plant extracts requires detailed investigation. However, in the absence of calcium ions from the medium, both extract amd AQ fraction tested at 2 mg/mL, did not potentiate oxytocin (Panel C: 3A-C) as evident in amplitude values (Panel C: Figure 3C) in a manner similar to *Justicia flava* leaf methanol extract [9]. This implies the relevance of calcium ions in physiological solution for elicitation of meaniingful tissue contraction. Kupittayanat *et al.* [15] have suggested the relevance of Ca^{2+} in uterine contractility.

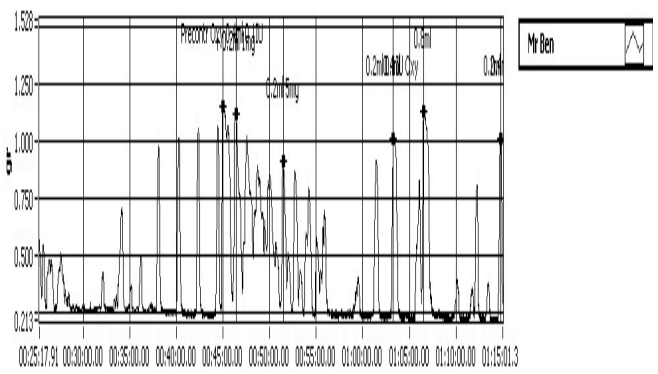

Figure 2A. Chart recording of Opuntia ficus-indica (OFI) extract on oxytocin pre-contracted uterus.

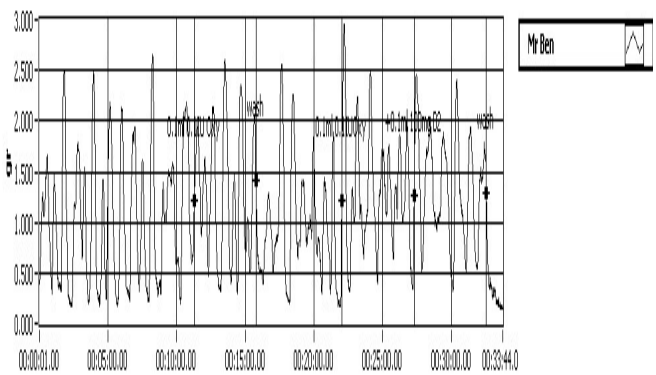

Figure 2B. Chart recording of AQ fraction of OFI on oxytocin pre-contracted uterus.

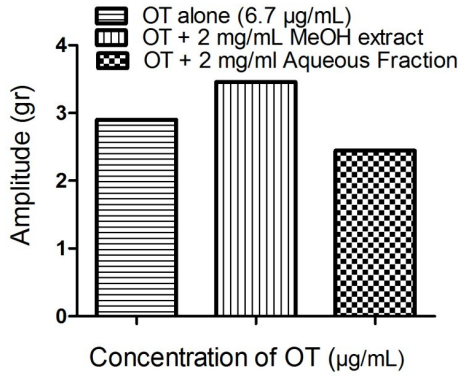

Figure 2C. Effect of Opuntia ficus-indica (OFI) on amplitude in oxytocin-precontracted uterus.

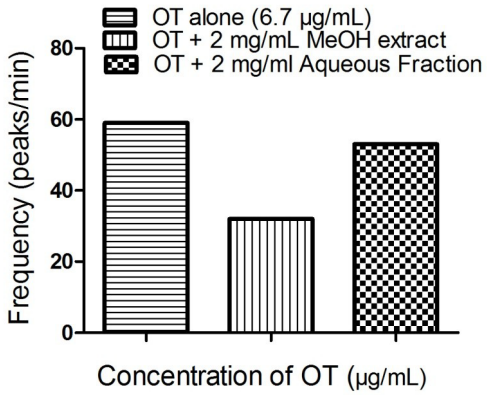

Figure 2D. Effect of OFI on frequency in oxytocin-pre-contracted uterus.

PANEL B: Effect of Opuntia ficus-indica on oxytocin-precontracted uterus.

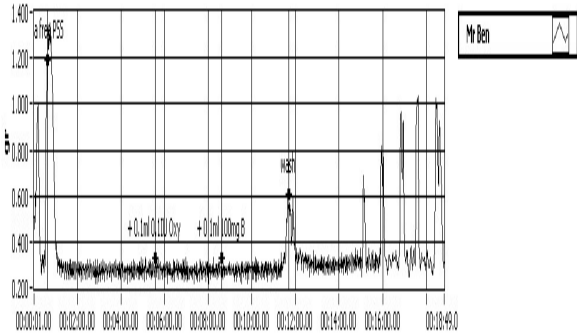

Figure 3A. Chart recording of crude extract of Opuntia ficus-indica (OFI) on oxytocin precontracted uterus in Ca^{2+}-free medium.

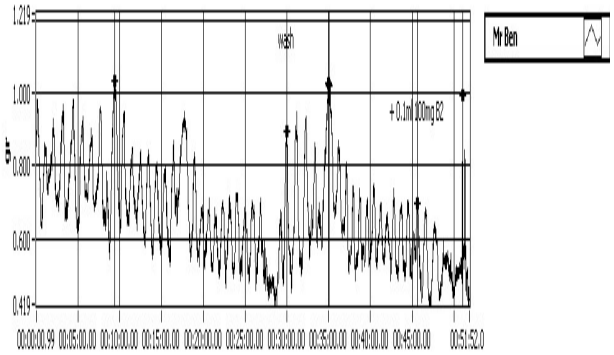

Figure 3B. Chart recording of AQ fraction of OFI on oxytocin precontracted uterus in Ca2+-free medium.

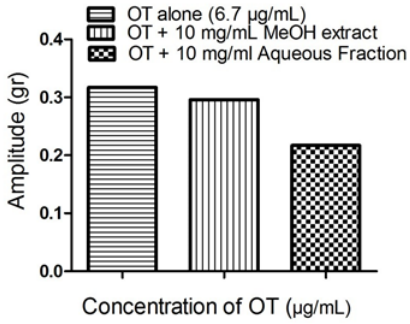

Figure 3C. Effect of OFI on amplitude in oxytocin precontracted uterus in Ca free-medium.

PANEL C. Effect of *Opuntia ficus-indica* on oxytocin precontracted uterus in Ca^{2+}-free medium.

In addition, the two tested agents in this study also failed to potentiate effect of high KCl induced uterine contraction (Panel D: Figures 4A-C). Extract gave greater inhibition (55.09%) in amplitude than AQ fraction (Figure 4C), signifying a different mechanism of uterine contraction action from KCL. KCL was reported to stimulate uterine tissue contractions by activating L-type voltage-gated calcium channel leading to sustained tissue depolarization [9], and thereby functions as an agonist. Bioactive flavonoids from

Ficus exasperata leaf methanol extract have been shown not to significantly inhibit KCL [8]. In another report by Bafor et al. [9], mechanism of inhibition of KCL and oxytocin contractility, as well as inhibition in Ca^{2+}-free PSS by plant extracts was via interaction with inositol triphosphate and ryanodine receptors and also through modulation of K^{+}-channels.

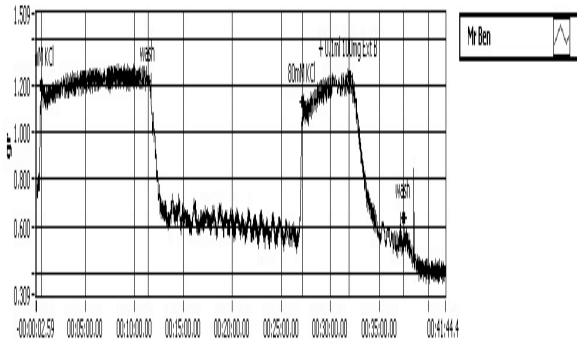

Figure 4A. Chart recording of Opuntia ficus-indica (OFI) extract on high KCL concentration-induced uterine contractility.

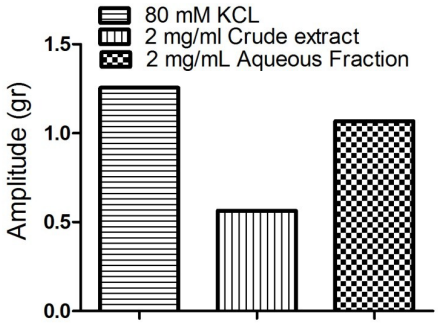

Figure 4C. Effect of OFI on amplitude in high KCL precontracted uterus.

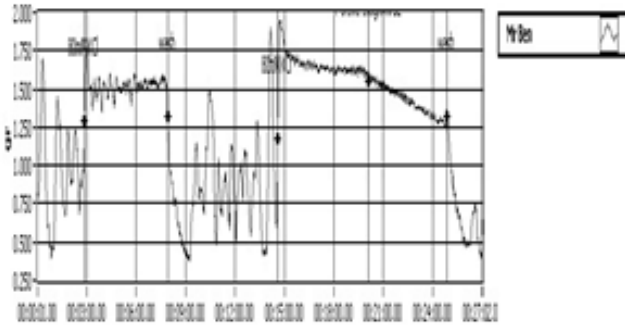

Figure 4B. Chart recording of AQ fraction of OFI on high KCL-induced uterine contraction.

PANEL D. Effect of Opuntia ficus-indica on high KCL precontracted uterus.

Results of the present study, being published for the first time, demonstrated oxytocin-like activities of *O. ficus-indica* stem in the estrogenized isolated rat uterus. Stem crude extract seems more potent than aqueous fraction in stimulating spontaneous contractions as well as potentiating oxytocin-induced contractions. Inhibitions of uterine contractions in high KCL concentration, and oxytocin-pre-contracted experiment in calcium-free medium by extract and AQ fraction were observed in this study. Phenols and flavonoids detected in the extract in this study, could be responsible for the observed oxytocic effect of *O. ficus-indica* [5]. Nevertheless, further phytochemical work is required to isolate oxytocic compounds from this plant.

Conclusion

This study justified the traditional significance of O. ficus-indica in facilitating childbirth in some African countries.

Conflict of interest

Authors declare no conflict of interest in this work.

Acknowledgements

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The effect of processed *Camellia sinensis* on acute amitraz poisoning in a rat model

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Abstract

Background: Amitraz is a formamidine derivative available as both an acaricide and an insecticide. Commercial formulations contain 12.5-20% of amitraz in xylene, propylene oxide or toluene. Triatix® is the most marketed brand in Kenya. Exposure to amitraz occurs through oral ingestion, skin contact or inhalation. Poisoning may be accidental or intentional. Intentional poisoning from amitraz has been on the rise especially in the agriculturally based communities and usually is through ingestion of undiluted amitraz product. Due to the lack of a specific antidote and management protocol, this presentation is mostly confused with organophosphate or carbamate poisoning and mostly managed symptomatically. However, it has been observed that co-administration of *Camellia sinensis* (tea) results in the worsening of the presenting symptoms and death.

Methodology: A correlational experimental study involving the use of Swiss albino female rats was done. The rats were divided into 6 groups receiving different treatments as water for injection, tea, amitraz (at 2 concentrations of 125 and 12.5mg/ml at a dose of 300mg/kg), and a combination of the 2 concentrations and tea. These were given as a single dose on the first day of study. The rats were observed for the presenting signs and their severity for 7 days. Management was done with intraperitoneal atropine, intravenous normal saline and warming.

Results: The study showed that both concentrations of amitraz produced a decrease in the general activity of these rats, with the central nervous system (CNS) symptoms manifesting rapidly and way before other organ pathologies. Tea worsened the presentation of amitraz as the manifestations were more severe and pronounced. The effects of the dilute concentration of amitraz with tea were more severe with coma and death occurring at 2.81 and 3.41hrs respectively in comparison to 5.14 and 6.18 hrs respectively for the undiluted concentration. The difference in the time to coma and time to death for the 2 concentrations was demonstrated to be statistically different using a t-test ($p < 0.05$).

Conclusions: Dilution of amitraz does not significantly affect the presentation of amitraz poisoning. However, the interaction that occurs with Camellia sinensis with dilution produces more severe effects. Thus, ingestion of tea worsens the presentation of amitraz poisoning by increasing the relative toxicity of amitraz in rats. Tea should be avoided in cases of suspected or diagnosed amitraz poisoning until full recovery.

Keywords: *Amitraz, Camellia Sinensis, Poisoning.*

Introduction

Hospitals worldwide handle numerous cases of poisoning, including acute, sub-acute, and chronic forms. Acute poisoning has become a significant cause of morbidity and mortality globally [1]. It is estimated that around 3 million acute poisoning cases occur each year, with approximately 220,000 resulting in fatalities. Human pesticide poisoning is one of the most prevalent forms of acute poisoning and has long been recognized as a serious public health issue. According to studies [1], as early as 1990, a World Health Organization (WHO) task force estimated that around one million cases of unintentional pesticide poisoning with severe symptoms occur each year, resulting in approximately 20,000 deaths. What is more staggering is the revelation by another study [2] that 95% of all fatal pesticide poisonings occur in developing countries. These cases arise from either deliberate or unintentional causes, with the majority being intentional attempts. It is estimated that about 30% of global suicide cases are due to pesticide self-poisoning. In children, poisoning cases often result from accidental exposure [3].

Amitraz poisoning in humans has been on the rise over the years due to several factors, including its widespread availability, increased use and exposure, and relatively low costs [4]. More men than women from agricultural communities are more affected due to their responsibility of spraying the farm with amitraz as a pesticide [3]. Amitraz is a formamidine derivative used as both an acaricide and an insecticide. It is employed to control ticks, lice, and manage mites in livestock and dogs, as well as pests in crops. Commercial formulations generally contain 12.5-20% amitraz dissolved or dispersed in organic solvents, primarily xylene [5].

Poisoning primarily occurs through oral, dermal, or inhalation routes, with oral exposure being the most common and causing more severe manifestations affecting several body organs. Poisoning results from both the solvent xylene and amitraz when exposed [6]. The poisoning cases from amitraz are often misdiagnosed as organophosphate poisoning due to the similarity of symptoms and the lack of

laboratory capacity to identify the toxicants. This leads to misidentification and misclassification of the toxic agent, or diagnosis based on clinical manifestations. Consequently, treatment is often incorrect, leading to deaths. Additionally, there is currently no known antidote for amitraz poisoning [4].

Therefore, supportive management and care are typically provided, including monitoring vital signs such as cardiovascular (CVS), central nervous system (CNS), and respiratory functions [3, 4]. The basic approach to management includes initial stabilization with intubation and ventilation support until the patient regains full consciousness. Most fatalities often occur due to respiratory depression. In some animal studies, α2-adrenergic antagonist yohimbine has shown to reverse most of the signs in amitraz poisoning acting as a possible antidote. However, no studies warrant its use in humans [7, 8].

Despite the high success rates in managing amitraz poisoning in health facilities, the use of tea has been identified to cause rebound effects that worsen the condition [9, 10]. This is particularly evident in patients who are awake and responding positively to treatment. Upon ingestion of tea, these patients may relapse into hypotension and coma, and if this is not promptly identified and corrected, it can result in death. Therefore, patients are often advised to avoid tea until they have fully recovered [11]. Tea is a common beverage, consumed by many people. It is not unusual to see tea being served to every patient each morning in hospitals. Given the frequent misdiagnosis of amitraz poisoning as organophosphate poisoning, carbamate poisoning or opioid overdose, tea is often served to these patients. This lack of knowledge might explain the high fatality rates involving pesticide poisoning in hospitals. For agricultural farmers using amitraz, chronic exposure could lead to chronic poisoning that develops over time, though this is rare. The daily dose of caffeine they consume each morning may hasten the presentation of symptoms or cause further damage to their organ systems, ranging from acute to chronic, or acute-on-chronic effects [12]. Studies on this interaction were lacking.

Camellia sinensis, the botanical name for tea, is an evergreen plant indigenous to Southeast Asia, primarily grown for commercial purposes. Tea is the second most consumed drink worldwide, after water. The various types of tea include black, white, green, oolong, pu-erh, fruit, herbal, and red tea, resulting from different processing techniques such as withering, crushing, rolling, oxidation and fermentation, drying, and sorting. Studies show that 95% of tea consumed in the UK is black tea [9, 10). Tea is associated with numerous medical uses and health-promoting benefits. Studies suggest it can lower the risk of cancer and coronary heart disease, improve oral health, protect against UV rays and osteoarthritis, and possesses anti-hypertensive, antimicrobial, antifibrinolytic, antitumor, antioxidant, and body weight control properties. These benefits are attributed to the polyphenol components of tea [9].

This study sought to determine the interaction between *Camellia sinensis* and the amitraz formulation when ingested together in a rat model. The results of the study aim to address this issue by disseminating knowledge to all institutions and individuals encountering amitraz poisoning as a medical case. It was intended to inspire further research to identify the responsible constituents, the mechanisms explaining this phenomenon, and any other drug interactions involving amitraz. Additionally, it is aimed at improving the management of amitraz poisoning and thus reducing the mortality rates associated with this type of pesticide poisoning.

Methodology

Study design

This study employed a correlational experimental study design. Both amitraz and tea were administered orally as a single dose on the first day of the study to several rats grouped into 6 groups. The rats administered with amitraz were managed for the presenting signs using atropine. These were observed for at most 7 days.

Study location

The zoology experimental animal room in Kenyatta University was used for the study. The temperatures were maintained at 25^0C and artificial lighting was provided to mimic the normal 12-hour day and 12-hour darkness. The animals were allowed free access to food and water.

Data variables

The independent variables in the study were: dose of tea, dose of amitraz and the fasted weight of the rats. The dependent variables were: Amitraz poisoning presentation, weight changes, outcome-dead or alive and the dose of atropine administered **(Table 1)**.

Table 1. Study variables

Variables	Indicators	Scale of measurement	Data collection technique	Source of data
Doses of atropine	Total Amount	Numerical	Calibrated syringe	Readings
Weight and weight changes	Difference between the fasted weight and the weight on day 7	Numerical	Weighing balance	Readings
Dose of treatment	Amount	Numerical	Calibrated syringe	Readings
Outcome	Alive/ dead, time to death	Categorical, numerical	Observations	Observations
Presenting signs and the severity of the symptoms	Intensity of the symptoms	Categorical	Observations, comparisons	Observations, inferencing

Test animals

Thirty (30) healthy Swiss white albino female rats of ages between 8-12 weeks were used in this study. These were obtained from the Kenyatta University biotechnology

laboratory. They were transported to the zoology experimental room a week prior the start of the study and allowed to acclimatize.

Amitraz formulation

Triatix® formulation batch number TRMR002, a product of Cooper K-Brands Ltd, Kenya, available as an emulsifiable concentrate containing 12.5%w/v amitraz in xylene was obtained from a veterinary shop in Nandi County, Kenya.

Processed tea

Unflavored Fahari® tea leaves of batch number 07/03:07, a product of Kenya Tea Packers Ltd was bought from a supermarket in Nandi County, Kenya.

Water for injection

An Apdl (Abacus Parenteral Drugs Ltd) product of batch number 800611 was obtained from a chemist near Kenyatta University. This was used as a solvent to dilute the concentrate and as a treatment for the negative control group.

Atropine

A sterile parenteral formulation of atropine of strength 1mg/ml, a product of Medisel (K) Ltd, batch number MD180102 was obtained from a pharmacy near Kenyatta university.

Rat food

The rats were allowed free access to rodent pellets and water.

Other solvents

99% chloroform for euthanizing all the treated animals and normal saline for fluid replacement.

Equipment

The equipment used included: weighing balance, timer, hot plate, measuring cylinder, rat cages with beddings, burning splint, calibrated syringes and needles, beakers, cotton wool, feeding tube and a stirring rod. These were pre-tested before the start of the study to ensure accuracy, validity and reliability.

Methods

The methodology was the acute oral toxicity Up-and-Down adopted from the OECD guidelines for the testing of chemicals 425 (2022).

Test procedure

The animals were fasted overnight prior to dosing where food was withheld, and water supplied. At the start of the study, the rats were weighed and divided into 6 groups receiving different combinations of drugs as:

A: Received water of injection

B: Received tea

C,D: Received amitraz at concentrations 125 mg/ml and 12.5 mg/ml respectively

E,F: Received tea and amitraz at the 2 different concentrations respectively

Preparation of amitraz and tea

Amitraz: Since 100ml of Triatix® contains 12.5g of amitraz, the dose in 1ml equals 125mg. One (1) dilution created 2 doses as follows:

i. 125 mg in 1ml

ii. Added 9 ml of water to the concentration in (i) above- 125mg in 10ml

Tea: Preparation involved boiling two (2) teaspoonfuls of Fahari® tea leaves in 250ml of water. This was left to settle and cool before being administered to the test animals.

Administration of amitraz and tea to the animals

Amitraz, tea and water were administered by gavage using a stomach tube. These were given as a single dose on the first day of study. To the groups receiving both tea and amitraz, the tea was administered an hour after the administration of amitraz. All the rats were monitored and treatment with intraperitoneal atropine was started immediately the rats showed severe manifestations of poisoning.

- Volume of amitraz administered: =body weight (kg) × Dose (300mg/kg) /concentration (mg/ml)
- Volume of atropine administered: =body weight (kg) × Dose (1mg/kg) /concentration (1mg/ml)
- Volume of tea and water for injection administered: =body weight (g) × 2mls /100g

Observation

Every rat was observed for the first seven (7) hours and daily for 7days. Body weights were recorded daily. The rats were fed with rat pellets and water throughout the course of the study. Additionally, intravenous normal saline and warming was provided to the rats in coma. At the end of the study, all the rats that were alive were sacrificed by euthanization with 99% chloroform.

Data management and analysis

Individual animal data was collected daily, and these summarized in a tabular form showing the type and volume of treatment given, the weight of the rat, doses of atropine injected and the general observed effects of the treatment including their effects on the activity of the rat. This data was summarized in tables as mean volumes, weights and weight changes, the number of alive and dead animals and the effects of the treatment on the physiological rat activities for the respective groups. This data was entered and stored in Google drive and subjected to analysis with both MS Excel® and the t-test.

Results

Acute effects of amitraz poisoning

Amitraz reduced the general activity of the rats with respiratory and CNS depression, and increased body secretions. Tea on the other hand increased the rats' activity and their breathing. A combination of the two treatments increased the intensity of amitraz intoxication manifestations.

The results are shown in **table 2** below.

Table 2. Observed effects with the different treatments.

Group	Observed effects
A- water for injection	Normal activity- including feeding, movement, breathing, stool, etc.
B- tea	Fast breathing, increased activity, tail elevation
C- 125mg/ml amitraz	Immediate tail elevation, mouth itching, drooping head, reduced activity, drowsiness, crowding and coldness to touch, heavy and strained breathing, general debilitation and staggering, tremors, reduced feeding, decreased defecation with loose and smelly stool, increased urine output, loose skin, death, aggressiveness to handling days after amitraz dose.
D- 12.5mg/ml amitraz	Immediate tail elevation, mouth itching, drooping head, reduced activity, drowsiness, crowding and coldness to touch, heavy and strained breathing, tremors, loose skin, general debilitation and staggering, increased nasal secretions, reduced feeding and defecation, increased urine output, coma and death
E- 125mg/ml amitraz + tea	Immediate tail elevation, mouth itching, drooping head, reduced activity and drowsiness, heavy and strained breathing, tremors, general debilitation and staggering, crowding and coldness to touch, bulged eyes, increased nasal secretions, loose skin. Immediately after tea administration, the activity increased for a few minutes with increased movements and then reduced with severe manifestations- gasping, increased nasal secretions, bulged eyes, tremors. Coma and death ensued within hours.
F- 12.5mg/ml amitraz + tea	Immediate tail elevation, mouth itching, drooping head, reduced activity and drowsiness, heavy and strained breathing, tremors, general debilitation and staggering, crowding and coldness to touch, bulged eyes, increased nasal secretions, loose skin. Immediately after tea administration, the activity increased for a few minutes with increased movements and then reduced with severe manifestations- gasping, increased nasal secretions, bulged eyes, tremors. Coma and death ensued within hours.

Effects of *Camellia sinensis* (tea) at different concentrations of amitraz

The average weight change for the group that received water for injection was relatively equal to that of tea group and more than 5 times that of 125mg/ml amitraz group (Table 3). No animal survived for the groups that received 12.5mg/ml amitraz and the two groups receiving both amitraz and tea. The t-test demonstrated a statistical significance in the difference in that the average weight gain in the rats after amitraz administration ($p<.001$). The time to coma, with co-administration of tea and 125 and 12.5mg/ml amitraz ($p<.05$) and the time to death with co-administration of tea with 125 and 12.5mg/ml amitraz ($p<.05$) were also significant.

Table 3. Summary of the effects of the different treatments

Group	A	B	C	D	E	F
Treatment	Water for injection	Tea	125mg/ml amitraz	12.5mg/ml amitraz	125mg/ml amitraz	12.5mg/ml amitraz
Average vol (mls)	2.3	2.2	0.29	2.5	0.26 1.9	2.4 2.2
Average wt (g)	119.5	114	126.5	107.5	112.5	111.5
Average wt change by day 7(g)	+42.75	+41.33	-	-	-	-
No. of animals dead	0	1	3	4	4	4
No. of animals alive	4	3	1	0	0	0
Average doses of atropine	-	-	5.5	8.5	5.5	7.25
Time to coma	-	-	-	2 only, average 2.6hrs	Average 5.14hrs	Average 2.81hrs
Time to death	-	day 4	2 died on day 1, 1 on day 3, 1 lived to day 7	2 died within 3.77hrs, 1 on day 1, 1 on day	Average 6.18hrs	Average 3.41hrs

Discussion

The pretest was conducted five days prior to the actual study. The aim was to determine whether the rats responded to amitraz and the dose at which the effects were observable. From this, the dose was set at 300 mg/ml of amitraz, half of the lethal dose. To avoid large and divided doses, only two concentrations were chosen: 125mg/ml and 12.5mg/ml. Due to the risk of inducing respiratory defects with per oral administration, the treatments were administered only on the first day of the study. Atropine was administered when manifestations worsened.

Both concentrations of amitraz produced a decrease in the general activity of the rats, including reduced movements, weakness, inability to support their weight, drowsiness, and eventually coma and death. Immediately after the administration of amitraz, their tails were elevated, their mouths itched, and their heads drooped. They crowded in the corners and were cold to the touch. Their breathing was heavy and somewhat strained. Other observed symptoms included increased nasal secretions, decreased defecation with loose and smelly stool, increased urination, and body tremors. They were alert and sensitive to pain. These effects correspond to the α-1 and α-2 adrenergic stimulation by amitraz [13].

The overall weight gain was statistically significantly lower than that of the corresponding control groups. This could be explained by the reduced food and water consumption. Their skins were loose, and their bodies appeared shrunken, which could signify organ atrophy. After recovery, the rats were hypersensitive to touch and became aggressive, indicating that the CNS was affected. The weights of the rats significantly influenced their response. Rats with smaller weights responded very quickly, experienced severe manifestations, fell into a coma, and died within hours, much earlier than those with larger weights. The weight cutoff was about 100 grams, with those weighing less than 100 grams showing a very rapid and severe response. Since rat weight is proportional to their age, this severity in low-weight rats suggests that the condition will be more severe in children than in young adults.

Dilution of amitraz showed no significant effect on the response of the rats to amitraz poisoning. The response to both concentrations was rapid. Symptoms were not reversible with atropine treatment, but rats treated with

atropine, provided with intravenous normal saline, and kept warm had a better outcome, demonstrating the effectiveness of symptomatic management of amitraz poisoning.

Generally, the effects on the central nervous system were rapid and intense, while effects on other organ systems occurred later. Atropine alone was not sufficient to reverse the effects of amitraz poisoning, though it did help manage bradycardia. Fluid support and warming were also inadequate on their own. Breathing support was seen to be a major requirement, as respiratory distress was severe. Regular monitoring of vital signs, including breathing, temperature, and heart rate, and more intensive management are required to treat this condition.

Tea demonstrated an increase in the activity of the rats with heightened breathing. The *Camellia sinensis* extracts, including flavonoids and alkaloids such as catechins, theophylline, and caffeine, inhibit phosphodiesterase enzymes, causing nitric oxide mediated vasodilation with relaxation of bronchial musculature, tachycardia, irritability, seizures, and nasal congestion [14]. Upon administration of amitraz, the rats showed a significant decrease in activity and general debilitation. However, after the administration of tea, their activity initially increased. Despite weakness, their movements increased, but then their activity reduced within a few minutes, and they succumbed to the toxic effects of amitraz. The manifestations became more severe and pronounced, with an increased number and intensity of body tremors, worsened breathing with gasping, greatly reduced bowel movements, looser stool, increased nasal secretions, and urination. The rats fell into a coma within hours, and death occurred on the first day of the study. No rat survived. This indicated an exaggeration of amitraz intoxication, suggesting a synergism between *Camellia sinensis* and amitraz.

The response to the two concentrations of amitraz was calculated to be statistically significantly different. With 12.5 mg/ml, more doses of atropine were used, and the time to coma and death was significantly shorter than with 125 mg/ml. The effects of the diluted concentration of amitraz with tea were more severe, with coma and death occurring at 2.81 hours and 3.41 hours, respectively, compared to 5.14 hours and 6.18 hours for the undiluted amitraz, as observed in this study. This demonstrates the significance of dilution, suggesting that dilution potentiates the interaction by providing more amitraz molecules and probably increasing their kinetic energies. Overall, tea worsened the presentation of amitraz poisoning. The manifestations were more severe and pronounced, with the effects being worse with the diluted concentration of amitraz compared to the undiluted.

Conclusion

The findings of this study lead to several compelling conclusions. First, the effects of amitraz poisoning on the central nervous system are rapid and intense, occurring before impacts on other organ systems, manifesting as α-1 and α-2 adrenergic stimulation. Second, while the dilution of amitraz does not significantly alter the presentation of amitraz poisoning on its own, it significantly affects the interaction with Camellia sinensis. Finally, tea exacerbates the presentation of amitraz poisoning, increasing the relative toxicity of amitraz in rats. These insights underscore the critical need for heightened awareness and careful management of amitraz poisoning, especially in contexts involving the consumption of tea.

Recommendations

Future research should focus on assessing the type of interaction that occurs between tea and amitraz, determining the effects of tea on amitraz poisoning at different time intervals (including before, during, and after intoxication), and further evaluating the effects of more dilute concentrations of amitraz. For future practice, there is a need to develop a better management protocol for amitraz poisoning that includes an effective antidote to fully reverse its effects. Moreover, it is crucial to avoid tea consumption in cases of both suspected and diagnosed amitraz poisoning until full recovery is achieved.

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Prevalence and determinants of Adverse Drug Events among HIV-Infected patients on Anti-Retroviral therapy in a Kenyan tertiary hospital

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Abstract

Background: HIV infection remains a threat to public health. Management of Human immunodeficiency virus infection normally includes multiple antiretroviral drugs and the potential for high drug toxicity. Understanding the prevalence and determinants of adverse drug events (ADEs) can inform clinical decision-making and improve patient outcomes.

Objective: To assess the prevalence and determinants of adverse drug events among patients on antiretroviral therapy in a Kenyan tertiary health facility.

Methodology: A descriptive cross-sectional study was carried out at the comprehensive care center of Kenyatta National Hospital. The target population was the adult patients infected with Human Immunodeficiency Virus and on antiretroviral care (ART). Data was collected from three hundred and seventy-one records of the patients that met the inclusion criteria. It was recorded in a structured form to capture the variables of interest. Data analysis was done using descriptive and inferential statistics at a 0.05 level of significance. STATA version 14 statistical software was used to analyze the data.

Results: The study comprised of 371 participants and 241 (58%) were females. The mean age was 43.3years (±11.5 SD) and the majority of the participants were married. The most commonly prescribed regimen was TDF/3TC/EFV. Hypertension (31, 8.3%) and tuberculosis (28, 7.6%) were the most common comorbidities. The most prevalent adverse drug events were itchiness (20, 5.4%), headache (20, 5.4%), rash (18, 4.9%) and peripheral neuropathy (17, 4.6%). The predictors of adverse drug events were regimen change (p= 0.03), history of drug allergy (p= 0.002) and presence of comorbidities (p=0.02).

Conclusion: The determinants of adverse drug events are varied. They include both patient and drug related factors.

Key words: *Adverse drug events, Anti-retroviral therapy, HIV infection, Determinants.*

Introduction

The main purpose of antiretroviral therapy (ART) is to suppress viral replication and reduce viral load to undetectable levels. ART is now recommended for all patients who test positive for Human Immunodeficiency Virus [1]. It facilitates the restoration and preservation of the immunological function of the body, reduction of Human Immunodeficiency Virus (HIV) related morbidity and mortality as well as improvement of the health-related quality of life. The management of patients infected with HIV constitutes the use of a combination of at least three drugs from different classes and therefore the occurrence of adverse drug events is plausible which may compromise the effectiveness of therapy. Adverse drug events (ADEs) may result in discontinuation of therapy, treatment interruption, regimen switch, poor adherence, and significant reductions in health-related quality of life [2]. Adherence is key in ensuring effective treatment that may be compromised because of adverse events which should be minimized or avoided. Patients infected with HIV have an increased potential for negative drug-to-drug interactions and comorbidities, resulting in increased risk for ADES, and this may complicate therapy [3]. Sometimes it may be difficult to distinguish the symptoms related to disease progression from ART adverse effects. This is because as the disease advances to Acquired Immune Deficiency Syndrome (AIDS), opportunistic infections are common and some of their symptoms resemble those due to ADEs due to ART. The risk of ADEs is, as a result of , HIV disease effect on the immune systems and the safety profiles of the complex anti-retroviral agents [4]. A number of toxicities and adverse effects associated with ART have been observed and associated factors documented [5]. Identification of these factors before and/or during treatment results in the prevention or reduction of the occurrence of unwanted drug events. These undesirable drug events are among the common causes for poor adherence to treatment [6]. This study sought to assess the magnitude and determinants of ADEs due to ART in HIV infected patients.

Methodology

Study design and area

This was a cross-sectional study. It involved collecting data from the patients' medical records. The study was conducted at the Comprehensive Care Centre (CCC) of the Kenyatta National Hospital (KNH). The hospital is the largest health facility in Kenya. It offers preventive, curative and clinical diagnostic health services. Its choice was informed by the availability of a sizeable number of patients presenting with HIV/AIDS. At the clinic, all the patient data were stored in a computerized database which was easily retrievable.

Study population

Patients above 18 years old attending CCC and were on anti-retroviral therapy were included. Their medical records were perused and the data collected using an abstraction form. Only complete medical records with the required data were considered.

Sample size and sampling technique

The medical records to be included in the study were selected through simple random sampling. A list of all patients on ART at KNH CCC was prepared and the records to be reviewed were chosen. The selected patients' records which met the inclusion criteria were reviewed. Using Fischer's formula, the sample size was computed. Three hundred and seventy one files were retrieved from the electronic data base.

Data collection

A designed data abstraction tool was used to extract the required information from the electronic medical records. The tool was designed into four sections. Section one was about participants' socio-demographic factors including age, sex, occupation, marital status, weight, height, alcohol consumption, and smoking status. Section two captured important clinical data such as ART regimen type, duration of therapy, concomitant medications, opportunistic infections, and comorbidities as well as laboratory data including CD4 count, viral load, and hemoglobin levels among others. Section three was designed to capture the various adverse drug events. The data abstraction tool was pretested on thirty medical records. This was done by comparing the data available in the medical records and the pre-determined ones. Any mismatch was corrected to ensure that all the relevant data was captured to increase the validity and reliability of the tool.

Data management

Data was entered into Epi-Info and then exported to the STATA statistical software version 14 for cleaning and analysis. Privacy was maintained by limiting access to the data collection tool to the relevant people only and using a computer password. Any data that might identify the patient were not recorded. Codes were used instead of patient identifier information. Data cleaning was done by checking any inconsistencies and missing information. Accuracy was observed by double-checking the recorded information. Data analysis was done using descriptive and inferential statistics at a 0.05 level of significance.

Logistical and ethical consideration

Ethical approval to conduct the study was obtained from UON/KNH ethics and research committee Authorization to use the medical records was sought from the KNH and the CCC management. Password to access the data was provided by the head of the data unit at the CCC. Confidentiality was ensured by avoiding recording the patient name on the data collection tool and protecting the entered data in the computer with a password.

Results

Socio-demographic characteristics of the study population

Data was collected from 371 patients' medical records. There were more females (241, 65%) than males (130, 35%) as shown in Table 1. The mean age was 43.3 years (SD± 11.5) and the range was 18.6 to 80.1 years. The majority (228, 61.5%) of the patients were between 36-55 years. Two hundred and ten (56.6%) patients were married. The mean weight was 70.2 kg (SD±14.5) and the mean BMI was 25.9(SD ± 5.2). One hundred and sixty-four (44.2%) participants had normal BMI.

Table 1. Socio-demographic characteristics of the study participants (n =371).

Variable	Category	Frequency (n)	Percentage (%)
Sex	Female Male	241 130	65 35
Age (years)	18-35 36-55 56-65 >65	94 228 32 17	25.3 61.5 8.6 4.6
Marital status	Married Single	210 161	56.6 43.4
Body mass index	Normal Overweight Obese Underweight	164 106 87 14	44.2 28.6 24.5 3.8
Alcohol consumption status	ever	21	5.7
Smoking status	ever	11	3.0
Duration of therapy (years)	Below 1 1-2 3-5 6-10 Above 10	15 33 104 156 63	4 9 28 42 17
WHO clinical stage of HIV	1 2 3 4	281 44 36 10	75.7 11.9 9.7 2.7
CD4 count	0-100 101-200 201-400 401-500 Above 500	20 28 96 52 175	5.4 7.5 25.9 14 47.2
Viral load	0-50 51-400 401-1000 Above 1000	321 24 5 21	86.5 6.5 1.4 5.6

Comorbidities	Hypertension	31	8.3
	Tuberculosis	28	7.6
	Diabetes mellitus	9	2.4
	Hypertensive renal disease	2	0.5
	Malignancy	6	1.6
	Diabetes mellitus and hypertension	5	1.3
	Arthritis	2	0.5
	Others	4	1.1

Sixteen (4.3%) patients were on therapy for less than a year. A total of 175(47.2 %) study subjects had a CD4 count above 500 cell/ mm3.

Only 21(5.7 %) participants had a history of alcohol intake and 11 (3.0 %) of smoking. The mean duration of ART therapy for the study participants was 6.6 years (SD ±3.5) and the range was 0.5 to 14 years. Two hundred and eighteen (58.8%) participants were on therapy for more than 5 years. The number of patient with a CD4 count of fewer than 100 cells/ mm3 was 20(5.4 %). Three hundred and twenty-one (86.5%) patients had an undetectable viral load of below 50 copies per ml. The most common comorbidities were hypertension (31, 8.3%) and tuberculosis (28, 7.6%). The majority (281, 75.7%) of the patients were at the early stages of the HIV disease and 10 (2.7%) of them had advanced disease.

The regimens that were used by the patients are shown in Table 2. Most (215, 58%) patients were on Tenofovir-based regimens mainly TDF/3TC/EFV followed by Zidovudine-based regimens while Abacavir-based regimens were the least prescribed.

Table 2. ART regimens prescribed to the study participants

Regimen	Frequency (n)	Percentage
TDF/3TC/EFV	215	58.0
TDF/3TC/NVP	38	10.2
AZT/3TC/EFV	26	7.0
AZT/3TC/NVP	25	6.7
TDF/3TC/LPVR	14	3.8
AZT/3TC/LPVR	14	3.8
TDF/3TC/ATVR	13	3.5
TDF/3TC/DGT	8	2.2
AZT/3TC/ATVR	6	1.6
AZT/3TC/EFV	5	1.4
ABC/3TC/EFV	4	0.3
ABC/3TC/LPVR	1	0.3
ABC/3TC/ATVR	1	0.3
ABC/3TC/DGT	1	0.3
DAR/RAL3TC	1	0.3
Total	**371**	**100.00**

Key: AZT-Zidovudine; ABC-Abacavir; 3TC- Lamivudine; DAR-Darunavir; DGT-dolutegravir; EFV-Efavirenz; TDF-Tenofovir

Prevalence of adverse drug events

The most commonly occurring adverse drug events (ADEs) were a headache and itchiness which were experienced by 20 (5.4 %) patients followed by skin rash which was reported by 18 (4.9 %) patients (**Table 3**).

Table 3. Prevalence of adverse drug events (n=371)

Adverse event	Frequency	Percentage
Headache	20	5.4
Itchiness	20	5.4
Rash	18	4.9
Peripheral neuropathy	17	4.6
dizziness	16	4.3
Nausea and vomiting	15	4.0
Abdominal pain	12	3.2
Diarrhoea	10	2.7
Hyperacidity	10	2.7
Anaemia	8	2.2
Bloating	8	2.2
Lipodystrophy	8	2.2
Numbness	8	2.2
Weight loss	7	1.9
Lipoatrophy	4	1.1
Hepatic derangements	4	1.1
Myalgia	4	1.1
Redness of skin	3	0.8
Hypersensitivity reaction	3	0.8
Blurred vision	3	0.8
Arthralgia	2	0.5
Amenorrhea	2	0.5
Gynecomastia	2	0.5
Drowsiness	2	0.5
Reduced appetite	2	0.5
Renal derangements	2	0.5
Tingling sensation	2	0.5
Varicose veins	2	0.5
Others*	10	2.7

Others*- include constipation, increased appetite, thrombocytopenia, hyperglycemia, hyperlipidemia, bone disorders, confusion, dyspepsia, and insomnia.

The various adverse drug events were grouped according to the ART regimen used (Table 4). TDF/3TC/EFV was associated with the most ADEs including nausea/vomiting, diarrhoea, itchiness, headache and dizziness among others. Rarely occurring ADEs like amenorrhea was associated with tenofovir-based regimens. Some cases of gynecomastia were also observed in participants on tenofovir-based regimens.

Table 4. Summary of ADEs associated with different ART regimens.

ART Regimen	Adverse drug Events
TDF/3TC/EFV (n=215)	N/v 9(4.2%), Diarrhea 5(2.3%), itchiness 10(4.7%), rash 7(3.3%), redness 1(0.47%), hypersensitivity 1(0.47%), headache12 (5.6%), dizziness 8(3.7%), weight loss 6(2.8%), lipodystrophy 5(2.3%), lipoatrophy 2(1%), peripheral neuropathy 6(2.8%), tingling 1(0.5%), numbness 4(1.9%), arthralgia 1(0.5%), insomnia 1(0.5%), myalgia 1(0.5%), effects 1(0.5%)
TDF/3TC/NVP (n=38)	N/V 2(5.3%), diarrhea 2(5.3%), itchiness 3(7.9%), rash 3(7.9%), headache 1(2.6%), dizziness 1(2.6 %), drowsiness 1(2.6%), lipodystrophy 1(2.6%), lipoatrophy 1(2.6%), peripheral neuropathy 2(5.3%), varicose veins 1(2.6%), amenorrhea 1(2.6%), hepatic effects 1(2.6%), renal effects 1(2.6%)
AZT/3TC/EFV (n=26)	Diarrhea 1 (4%), itchiness 2(7.7%), rash 2(7.7%), headache 1(3.8%), peripheral neuropathy 2(7.7%), tingling 1(3.9%)
AZT/3TC/NVP (n=25)	Headache 1 (4%) anemia 4(16%), numbness 1(4%), varicose veins 1(4%)
TDF/3TC/LPVr (n=14)	Diarrhea 1 (7.1%), itchiness 1(7.1%), rash 2(14.3%), hypersensitivity (7.1%), peripheral neuropathy 2(14.3%), dyspepsia 1(7.1%), amenorrhoea1 (7.1%), bone disorders 1(7.1%)
AZT/3TC/LPVr (n=14)	Itchiness 2(14.3%), rash 2(14.3%), redness 2(14.3%) hypersensitivity (07.1), dizziness 2(14.3%), anemia 1(7.7%), lipoatrophy 2(1%), peripheral neuropathy 1(7.1%), numbness 1(7.1%), arthralgia 1(7.1%), myalgia 2(14.3%)
TDF/3TC/ATVr (n=13)	N/v 1(7.7%), diarhoea 1(7.7%), rash 1(7.7%), headache 4(30.8%), 1(7.7%), drowsiness 1(7.1%), anemia 1(7.7), weight loss 1(7.7%), lipodystrophy 1(7.7%), peripheral neuropathy 1(7.1%), hepatic effects 1(7.7%)

AZT/3TC/ATVr (n=6)	N/v 1(16.7%), Itchiness 1(16.7%), rash 1(16.7%), dizziness (16.7%) peripheral
TDF/3TC/DGT (n=8)	N/v 1(12.5%), itchiness1 (12.5%), dizziness 1(12.5%), peripheral neuropathy (12.5%), numbness 1(12.5%), gynecomastia 1(12.5%), hepatic effects 1(12.5%)

Key: AZT-Zidovudine; ABC-Abacavir; 3TC- Lamivudine; DAR-Darunavir; DGT-Dolutegravir; EFV- Efavirenz; TDF-Tenofovir.

Peripheral neuropathy was mostly associated with tenofovir and zidovudine-based regimens. Fat mal-distribution occurred in patients on different regimens.

Determinants of adverse drug reactions

Bivariable and multivariable analyses were carried out using logistic regression to establish the predictors of ADEs at 0.05 level of significance and the results are shown in **Table 5**.

Table 5. Logistic regression analysis of independent determinants of ADEs

Variable	Bivariable analysis		Multivariable analysis	
	COR (95% CI)	P value	AOR (95 %CI)	P value
Sex	0.679(0.428-1.079)	0.101	0.357(0.718-1.776)	0.208
Age	0.669(0.496-0.903)	0.009*	0.684(0.284-1.645)	0.396
Marital status	1.575(1.021-2.429)	0.04*	1.350(0.322-5.656)	0.682
BMI	1.067(0.839-1.357	0.53	1.041(0.466-2.326)	0.921
Alcohol intake	0.767(0.290-6.443)	0.592	0.312(0.169-5.762)	0.435
Smoking	1.114(0.320-3.881)	0.865	12.724(0.56-289.32)	0.111
Regimen type	0.828(0.723-0.948)	0.006*	0.954(0.598-1.522)	0.842
Regimen change	3.875(2.257-6.653)	<0.001*	4.685(1.157-18.965)	0.03*
Comorbidities	0.839(0.707-0.994)	0.043*	0.769 (0.616-0.96)	0.02*
Concomitant meds	1.428(0.845-2.411)	0.183	4.548(0.751-27.529)	0.099
WHO stage	0.715(0.546-0.936)	0.015*	0.584(0.263-1.308)	0.191
Viral load	0.768(0.584-1.0110)	0.06	0.569(0.248-1.308)	0.184
CD4 count	1.129(0.950-1.342)	0.169	1.114(0.660-1.879)	0.686
ART duration	0.820(0.657-1.022)	0.077	1.103(0.546-2.227)	0.784
Drug allergy	6.931(2.211-21.732)	<0.001*	6.193(1.954-19.627)	0.002*
Adherence	0.656(0.352-1.224)	0.185	3.633(0.322-40.873)	0.296

*- Statistically significant P value

The presence or absence of ADEs was the dependent variable while other characteristics were the independent variables. Age was a predictor for ADEs (p= 0.009). Participants who were below 35 years old were 0.669 likely to develop ADEs as compared to those above 35 years. Marital status (p= 0.04) was associated with the development of ADEs with single participants 1.575 more likely to develop ADEs compared to the married participants. Regimen change was a strong predictor of ADE occurrence. Patients who had regimen changes were 3.875 more likely to experience ADEs (p= 0001). Development of ADEs was experienced more in patients who had advanced HIV disease (p= 0.015). ADE occurrence was strongly influenced by the type of ART (p= 0.006). Patients on TDF/3TC/EFV regimen were 0.89 times more likely to develop ADEs as compared to patients on other regimens. Those with a history of allergy to any drug were almost seven times more likely to experience ADEs (p =0.001). Multivariable logistic regression was carried out to determine independent predictors of the development of ADEs. They included regimen change (p= 0.03), comorbidities (p=0.02), and history of drug allergy (0.002).

Discussion

There were more females in this study than males [7]. Females have a higher risk of HIV infection due to their inequality in social, cultural, and economic status in society as well as the anatomy of their reproductive system. The majority of the study patients were in their middle age [8]. This age category is most affected by HIV infection because they are married people who are more at risk [9]. The most common regimen was TDF/3TC/EFV and this is consistent with the findings from two different studies carried out in Ethiopia [10].

The overall prevalence of adverse drug events varies according to place and population [11]. Most adverse drug events were associated with TDF/3TC/EFV. Peripheral neuropathy has been observed to be common due to the antiretroviral therapy as well as drugs used to treat opportunistic infections such as tuberculosis or advanced HIV disease [12]. Approximately one-third of patients on Nucleoside Reverse Transcriptase Inhibitors (NRTIs) develop neuropathies. The rash is a common reaction due to Non-Nucleoside Reverse Transcriptase Inhibitors(NNRTIs), especially Nevirapine [13]. Nausea and vomiting were also among the most frequently occurring ADEs and they can sometimes be serious to warrant discontinuation of therapy (14). Diarrhea, bloating, dyspepsia, hyperacidity, reduced appetite, and constipation were also reported.

The most common CNS disorder was a headache [14]. Other CNS symptoms observed were dizziness, blurred vision, drowsiness, confusion, and sleep disturbances [15]. CNS symptoms most commonly occur with the use of efavirenz and tenofovir. Few cases of lipid maldistribution dysfunctions were reported. They are associated with NTRIs and protease inhibitors [5]. There were very few cases of liver toxicity. Prevalence of hepatotoxicity may range from 1-29 % among patients on ART medications [16]. Liver disorders in HIV patients are associated with the use of NNTRIs, NRTIs, and Protein Inhibitors (PIs) and may also be due to the destruction of the liver by the HIV. It is worsened in co-infection with viral hepatitis [17]. Regular monitoring of liver enzymes should be incorporated as part of care in these patients. Renal toxicity was also prevalent to a small extent. In HIV-infected persons renal disorders are associated with nephrotoxic drugs like Tenofovir [18] or disorders such as dyslipidemia and hypertension. The only hematological disorder reported was anemia but the incidences were few because Zidovudine is usually the major culprit and it was not widely used.

Factors shown to be significantly associated with the development of ADEs include age, regimen change, WHO stage, and history of drug allergy. ADEs were more common in females than males. Development of ADEs is more likely to occur as age advances [19]. BMI, alcohol consumption, and smoking status relationship with ADEs was not statistically significant which contradicts findings from other studies [17]. The risk of experiencing ADE is higher in WHO clinical stages 2, 3, and 4 of HIV compared to stage one [20]. As the disease advances, patients develop some symptoms

that resemble drug toxicity. The type of regimen is also associated with specific ADEs [21,22]. Regimen change influences the occurrence of ADEs in that patients can develop them when they switch to new regimens due to other reasons like comorbidities or the development of toxicity. Comorbidities and the use of additional drugs together with ART medications increase the risk of adverse drug events [23].

Conclusion

The most common adverse drug effects involved the gastro-intestinal and nervous systems. Changes of ART regimen, comorbidities and drug allergy were the independent predictors of adverse drug reactions.

Recommendation

Screening, prevention and management of adverse drug events should be strengthened because the prevalence of ADEs was high. The patient data should be comprehensive to provide a holistic view which is essential in the management of HIV and associated illness.

Conflict of Interest declaration

The authors declare no conflict of interest.

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