African Journal of Pharmacology and Therapeutics Vol. 7 No. 1 Pages 7-12, 2018
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Research Article

Identification and characterization of potential drug interactions in hypertensive patients in a Kenyan tertiary hospital

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Background: Hypertensive patients are particularly at risk of drug-drug interactions resulting from the concomitant use of multiple drugs to control their blood pressure. The presence of comorbidities and advancing age are also likely to contribute to the use of many drugs, further increasing this risk. Drug related problems such as drug interactions in the management of hypertension increase morbidity and mortality but there are limited published data to characterize them especially among the African population.

Objective: To identify and characterize potential drug interactions among adult hypertensive patients attending Kenyatta National Hospital.

Methods: This was a descriptive cross-sectional study done among 313 adult patients between May to July 2016 at Kenyatta National Hospital. Ethical approval was sought from the institutional review board. Data on patient demographics, clinical characteristics and current prescriptions were extracted from patient records into predesigned data collection forms. Potential drug interactions were identified using an online Drug Interactions Checker.

Results: There was female predominance at 60.7% and the mean age of the study population was 55.2 years (SD 15.9). The mean number of drugs per prescription was 5.93 (SD 2.24). The prevalence of potential drug interactions was 92.7%. There was an average of 3.5 drug interactions per prescription. Majority (79.2%) of the potential drug interactions were categorized as moderate while major and minor interactions accounted for 4.1% and 16.8%, respectively. The most prevalent interacting drug pair was enalapril and furosemide (15.3 %). The most frequent major interaction found was between enalapril and spironolactone, which is associated with hyperkalaemia.

Conclusions: There was a high prevalence of potential drug interactions. Prescribers should be encouraged to be vigilant during the management of hypertensive patients to avoid overt drug interactions which may compromise treatment outcomes and increase the health care costs.

Keywords: Drug interactions, hypertension, prescriptions, Kenya

Received: October, 2017
Published: January, 2018

1. Introduction

Drug-drug interaction (DDI) occurs when two or more drugs are administered concomitantly and the pharmacological effects of one drug are altered by another. The result of the interaction would either increase or decrease the effect of the object drug, or produce a new and unanticipated effect of either drug (Baxter, 2010).

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DDIs are considered to be beneficial or harmful depending on the type of medication, or the indication (Reis and Cassiani, 2011). Problems arise when they cause an increase in morbidity and mortality, which could otherwise have been avoided. The harmful consequences of DDIs range from minor morbidities to fatal consequences, (Carter et al, 2002) such as hyperkalaemia, increased risk of asthma, increased risk of rhabdomyolysis or myopathy as well as increased risk of gastrointestinal haemorrhage (Bertoli et al, 2010; Bucsa et al, 2012).

The avoidance/prevention of DDIs and their potentially harmful outcomes is therefore a relevant clinical concern as this would decrease risk of avoidable adverse drug events in the patients, which in turn would decrease healthcare costs and shorten the length of hospital stay (Moura et al, 2009). Nonetheless, there is scarcity of studies that have attempted to quantify this.

DDIs may go unnoticed during prescribing. One of the attempts to address the problem of harmful DDIs has been the development of computerized software for checking drug interactions such as Medscape Drug Interaction Checker, Drug Interactions Checker, Micromedex, and LexiComp Interact. These utilities are able to detect potential drug interactions and hence guide the clinician in prescribing.

Hypertension is a global challenge with a study by Kearney *et al* projecting an increase to 29% of the world's adult population that will have hypertension by 2025. The burden of hypertension is even higher in economically developing countries than in economically developed countries (Kearney et al, 2005). In Kenya, studies on hypertension have shown a prevalence of 22.8% (Joshi et al, 2014). Studies in Africa, Asia and South America have shown that the prevalence of DDIs is high ranging from 30-80% (Reis and Cassiani, 2011; Moura et al, 2009; Lubinga and Uwiduhaye, 2011; Kothari and Ganguly 2014; Kigen et al, 2011). Hypertensive patients are particularly at risk due to the concomitant use of multiple drugs to control their blood pressure. The presence of comorbidities and advancing age are also likely to contribute to the use of many drugs, further increasing their risk of DDIs.

In Kenya, published studies on DDIs specifically in hypertensive patients are unavailable. This study sought to identify and characterize potential drug interactions among adult hypertensive patients at Kenyatta National Hospital (KNH) with an aim of raising awareness among physicians and pharmacists on the extent of the burden of DDIs among their hypertensive patients.

2. Methods

2.1 Study site and design

This was a descriptive cross-sectional study conducted among 313 freely consenting hypertensive patients aged 18 years and above who were either inpatients in medical wards or outpatients at the medical outpatient clinic of KNH, the largest National Referral and Teaching Hospital in East Africa with a bed capacity of 2000 beds distributed in 50 wards.

2.2 Study population and eligibility criteria

The study period for enrolment of patients was May to July 2016. Adult hypertensive patients of both sexes who visited the medical out-patient clinic or were admitted to the medical wards during the study period, who gave informed consent and whose prescriptions had more than one drug prescribed were included in the study. Any person who could not communicate effectively due to stroke was excluded.

2.3 Sample size and sampling procedure

Universal sampling was used whereby all eligible participants were included as they were identified. The final sample size achieved was 313, which was the minimum target sample size as calculated using the Fischer's formula (Daniel and Cross, 2013) with an estimated prevalence of DDIs among hypertensive patients of 71.5% (Kothari and Ganguly, 2014). From the medical outpatient clinic, 54 patients were sampled and 259 patients were enrolled from the 8 medical wards.

2.4 Data collection and study variables

Data on patient demographics, clinical characteristics, risk factors for polypharmacy, and current prescriptions were collected from the patient files. After receiving informed consent from the patients the researcher also conducted questionnaire-guided interviews at the patient's convenience.

The data collected from these interviews included patient demographics, risk factors, comorbidities and current medications. The interview was conducted in the available doctor's or nurse's room to ensure privacy.

2.5 Data analysis

Data analysis was done using STATA version 13 statistical software. The drugs prescribed to each patient were keyed into the online Drug Interactions Checker. The host website is a comprehensive and up to date source of drugs online, providing free, peer reviewed, accurate and independent data on more than 24,000 prescription drugs, over the counter medicines and natural products. This software classified the drug interactions as minor, moderate or major interactions and their outcomes.

Major interactions were defined as highly clinically significant where the combination should be avoided and the risk outweighed the benefit. Moderate interactions were defined as moderately clinically significant, with the combination usually avoided and only used under special circumstances. Lastly, minor interactions were defined as minimally clinically significant, where risk should be assessed and either an alternative drug considered, steps taken to circumvent the risk and/or a monitoring plan instituted. The noted drug interactions were classified, coded and recorded in terms of severity and the clinical outcome.

Descriptive statistics as frequencies, percentages, mean, standard deviation and range were calculated for the various variables and reported.

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2.6 Ethical considerations

Ethical clearance was sought from Kenyatta National Hospital/ University of Nairobi Ethics and Research Committee (KNH/UON-ERC), and approval was granted under study reference number **KNH-ERC/RR/271**. Permission to use patient files was sought from Kenyatta National Hospital Head of medical records. Informed consent was sought from the patients before administration of the questionnaires. Information obtained from the patients was kept in confidence and all data collection forms were coded to also maintain confidentiality. In cases of identified major DDIs, the prescriber was notified and a safer alternative recommended. The KNH reporting form for such interactions was filled and submitted to facilitate follow up.

3. Results

A total of 313 participants were included in the study. The mean age of the participants was 55.2 years (SD 15.9). The age ranged between 18 and 90 years but majority were above 38 years (**Table 1**).

Table 1: Characteristics of study participants

Variable	Frequency(n)	Percentage (%)
Gender		
Male	123	39.3
Female	190	60.7
Clinical setting		
Inpatient	259	82.8
Outpatient	54	17.2
Age Category (years)		
18-27	19	6.1
28-37	29	9.3
38-47	46	14.7
48-57	76	24.3
58-67	64	20.5
68-77	55	17.6
>78	24	7.7
Mean ± SD		55.2 ± 15.9
Range		18,90
Number of drugs prescribed per patient		
2-5	131	41.9
6-9	163	52.1
>9	19	6.1

The mean number of drugs per prescription was 5.93 (SD 2.24) and ranged from 2 to 16. Some of the predominant classes of drugs prescribed were calcium channel blockers (55%), angiotensin converting enzyme inhibitors/ angiotensin II receptor blockers (54%), loop diuretics (37.1%) and antibiotics (37.1%).

There were a total of 1086 DDIs identified in the 313 prescriptions, translating to approximately 3.5 DDIs per patient. These ranged from a minimum of 1 to a maximum of 12 per patient. Two hundred and ninety prescriptions (92.7%) had at least one DDI while 23 (7.3%) did not have any DDI (**Figure 1**).

The overall prevalence of moderate drug interactions was 88.5%, while the prevalence of minor and major interactions was 36.4% and 11.8, respectively. On average, there were 0.1 major, 2.7 moderate and 0.6 minor DDIs per patient. The highest number of major and moderate interactions seen in a patient was 2 and 10, respectively. Most prescriptions had moderate interactions only (49.8%), followed by prescriptions with both moderate and minor interactions with a prevalence of 27.5% as seen in **Figure 1**.

Overall, the predominant drug interacting pair was enalapril + furosemide (n= 48, 15.3%) as shown in **Table 2**. It was followed by omeprazole + furosemide, carvedilol + furosemide, omeprazole + nifedipine, insulin + furosemide and nifedipine + atorvastatin with prevalence of 38(12.1%), 37(11.8%), 37(11.8%), 32(10.2%) and 27 (1.9%) respectively.

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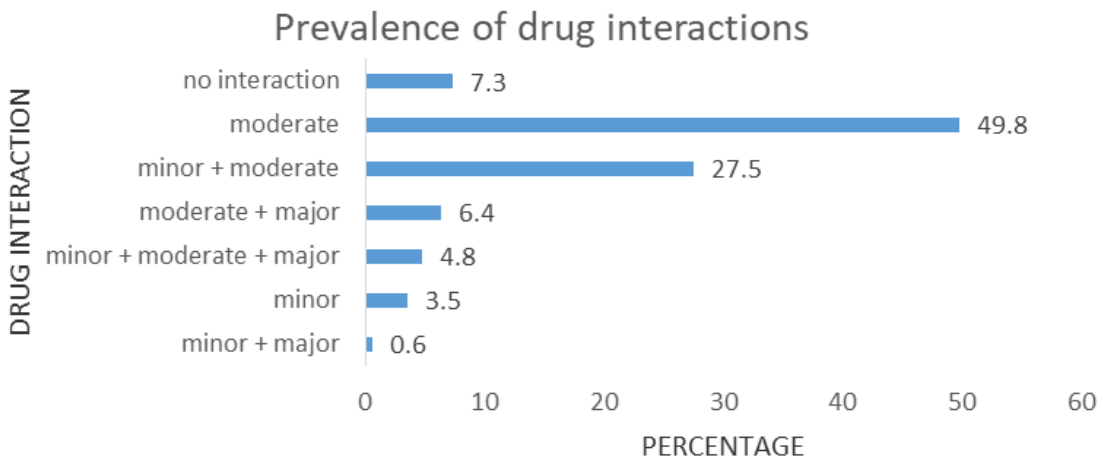

Figure 1: Prevalence of Drug Interactions

Table 2: Most prevalent interacting drug pairs and their potential outcomes

Drug pair	n (%)	Severity of Potential Interaction	Potential Outcome
Enalapril + Furosemide	48(15.3)	Moderate	Hypotension
Omeprazole + Furosemide	38(12.1)	Moderate	Hypomagnesemia
Carvedilol + Furosemide	37(11.8)	Moderate	Hypotension
Omeprazole + Nifedipine	37(11.8)	Minor	Hypotension, bradicardia, edema, dyspnoea, confusion, headache
Insulin + Furosemide	32(10.2)	Moderate	Hyperglycaemia
Atorvastatin + Nifedipine	27(8.6)	Moderate	Increased risk of rhabdomyolysis
Enalapril + Enoxaparin	22(7.0)	Moderate	Hyperkalaemia
Enalapril + Insulin	21(6.7	Moderate	Hypoglycaemia
HCTZ + Insulin	20(6.4)	Moderate	Hyperglycaemia
Carvedilol + Nifedipine	19(6.1)	Moderate	Hypotension
Carvedilol + Aspirin	19(6.1)	Minor	Decreased antihypertensive effect
HCTZ + Amlodipine	18(5.8)	Minor	Hypotension
Hydralazine + Furosemide	17(5.4)	Minor	Increased diuretic effect
Aspirin + Furosemide	17(5.4)	Minor	Decreased diuretic effect
Enalapril + Metformin	17(5.4)	Moderate	Hypoglycaemia
Enalapril + Aspirin	17(5.4)	Moderate	Decreased antihypertensive effect
Insulin + Carvedilol	17(5.4)	Moderate	Hypoglycaemia
Ceftriaxone + Furosemide	16(5.1)	Moderate	Nephrotoxicity
Omeprazole + HCTZ	16(5.1)	Moderate	Hypomagnesemia
Losartan + Aspirin	16(5.1)	Moderate	Decreased antihypertensive effect
Enalapril + HCTZ	15(4.8)	Moderate	Hypotension
Enoxaparin + Spironolactone	15(4.8)	Moderate	Hyperkalaemia
Losartan + Insulin	15(4.8)	Moderate	Hypoglycaemia
Carvedilol + Spironolactone	15(4.8)	Moderate	Hypotension

Furosemide and enalapril were the most common drugs implicated in DDIs. They were present in 310 and 239 interacting drug pairs, respectively (**Figure 2**).

The most prevalent major drug interacting pair was enalapril + spironolactone (n=23, 7.4%) as shown in **Table 3**.

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The other common major interactions were enalapril + trimethoprim and salbutamol + carvedilol, potentially causing hyperkalaemia and bronchospasms.

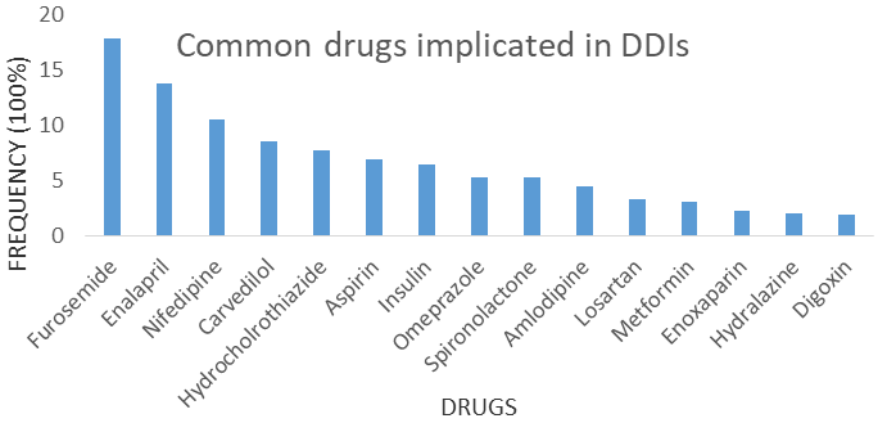

Figure 2: Common Drugs Implicated in DDIs

Table 3: Prevalence of major interacting drug pairs and their potential outcomes

Drug pair	n (%)	Severity of Interaction	Potential Outcome
Enalapril + spironolactone	23 (7.4)	Major	Hyperkalaemia
Enalapril + trimethoprim	4 (1.3)	Major	Hyperkalaemia
Salbutamol + carvedilol	4 (1.3)	Major	Bronchospasms
Enalapril + KCl	1 (0.3)	Major	Hyperkalaemia
Formoterol + Carvedilol	2 (0.6)	Major	Bronchospasms
Spironolactone + Losartan	3 (1.0)	Major	Hyperkalaemia
Enalapril + Losartan	1 (0.3)	Major	Hyperkalaemia
Nimodipine + Carbamazepine	1 (0.3)	Major	Decreased antihypertensive effect
Methyldopa + Carvedilol	2 (0.6)	Major	Hypertensive crises
Losartan + Trimethoprim	1 (0.3)	Major	Hyperkalaemia
Enalapril + Allopurinol	1 (0.3)	Major	Risk of infection, hypersensitivity reactions
Amlodipine + Simvastatin	1 (0.3)	Major	Rhabdomyolysis

4.0 Discussion

The prevalence of potential drug interactions was 92.7% which is much higher than that found by Kothari *et al* (Kothari and Ganguly, 2014). This difference could be attributed to the use of a different software (Medscape drug interaction checker) to identify drug interactions, the differences in the inclusion criteria for the study as well as a different study setting.

The present study reported furosemide and enalapril as the most common drugs implicated in DDIs, this was consistent with the study by Chelkeba *et al* in which enalapril was the commonest drug followed by Furosemide. Some of the other common drugs encountered in this study were nifedipine, carvedilol and hydrochlorothiazide. Although the most common drugs reported to be involved in DDIs in the study by Kothari *et al* were atenolol and aspirin, there was similarity in some of the common drugs reported like hydrochlorothiazide, enalapril and furosemide (Kothari and Ganguly, 2014).

In the present study, enalapril + furosemide was the most common interacting drug pair this was a similar finding reported by Chelkeba *et al*(Chelkeba et al, 2013). In the study by Kothari, the most common interacting drug pair reported was atenolol + amlodipine, but less common was enalapril + furosemide (Kothari and Ganguly, 2014). The implication of this finding is that although these drugs are commonly combined, patients must still be monitored for any signs of hypotension, decreased diuretic and antihypertensive effect and also hypokalaemia. Another study had a combination of a loop diuretic + ACE inhibitor and loop diuretic + NSAID as the most frequently occurring interacting drug pairs involving antihypertensive drugs (Lubinga and Uwiduhaye, 2011). Digoxin + furosemide was reported to be the predominant drug interaction in another study (Moura et al, 2009).

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In the present study, the most frequently occurring major interaction was enalapril + spironolactone, this was consistent with the study by Chelkeba *et al* (Chelkeba et al, 2013). Another major interaction that was reported in the present study was amlodipine + simvastatin, this was consistent with the study by Bucsa *et al* in which it was the most prevalent major interaction reported (Bucsa et al, 2012). The present study also reported a drug combination between salbutamol + carvedilol in 4 (1.3%) patients. This finding was similar to that by Bertoli *et al* that reported a combination of salbutamol + carvedilol in 2 out of 200 patients, which was also considered a major interaction with a potential outcome of bronchospasms (Bertoli et al, 2010).

Other drug combinations reported in the present study that were similar to the study by Bertoli *et al* were ACE inhibitor + antidiabetic with a potential outcome of hypoglycaemia, ACE inhibitor + potassium wasting diuretic with a potential outcome of hypotension and potassium wasting diuretic + corticosteroid that had a potential outcome of hypokalaemia. The implication of these findings is that although these drugs are commonly prescribed, patients must still be monitored for any signs of hypoglycaemia, hypotension and hypokalaemia.

5.0 Conclusion

There was high prevalence of potential DDIs. The predicted clinical implications of these interactions ranged from major ones such as hyperkalaemia and bronchospasms, moderate ones such as hypoglycaemia and hypokalaemia and minor ones such as decreased antihypertensive and diuretic effects. The implication of this finding would be the need to promptly detect such drug interactions and thus avoid any associated negative outcomes or monitor patients with caution. This can be done by use of a computerized software system that would aid in monitoring the patients effectively. Secondly, deployment of clinical pharmacists in all clinical areas will enhance vigilance and aid in detection of clinically relevant drug interactions which would decrease the risks involved as well as improve the quality of prescribing thus enhancing safer and the best management in the patient. The study design could only provide the prevalence of potential DDIs and not the actual outcomes of DDIs, which could form the subject for future studies.

Conflict of Interest declaration

The authors declare no conflict of interest.

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