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Adverse Drug Reactions and Drug-Drug Interactions with Cardiovascular Medications Seen in Patients Attending a Teaching Hospital in Ghana

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Abstract

Many pharmacological agents are usually combined to manage inflammation, haemodynamic and neurohormonal alterations which occur in patients with cardiovascular diseases (CVDs). Combination therapy usually results in undesired drug-drug interactions (DDIs) and adverse drug reactions (ADRs). The aim of this study was to determine the various DDIs and ADRs that occurred in patients with CVDs receiving pharmacological treatment at the cardiac clinic, Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana. Two hundred and forty-eight (248) patients were recruited for the study. Eligible participants were patients with heart failure, ischaemic heart disease or arrhythmias aged 13 years and above. ADR report involved documentation of adverse effects to previous cardiovascular therapy. ADRs were categorized based on the type of ADR, organ or system implicated, suspected medicine (s) that induced the effect and intervention provided to avert the problem. All medications prescribed during routine visit were also documented to assess for DDI. The prescription per patient were entered into an online medical information source (Medscape) to generate the interactions. The interactions were compared to Stockley's drug interaction, 9th edition (2010) and British National Formulary, 66th edition (2013/2014). A total of 19 ADRs were reported in 17 patients, that is 6.9% of the sample. The proportion of these ADRs were 17.6%, 35.3% and 49.1% for age ranges 30-49, 50-69 and 70-89 years with the average age of 65.2 years. More men reported ADRs with the ratio of men to women being 0.59:0.41. Aspirin recorded the highest percentage drug interactions (21.3%, n=43), followed by furosemide (11.4%, n=23) and bisoprolol (12.4%, n=25). Out of the 202 interactions, 152 (75.2%) of the interactions were significant whereas 37 (18.3%) and 13 (6.4%) were mild and severe respectively. Again, 122 (60.4%) of the interactions were pharmacodynamic interactions whereas 72 (35.6%) of interactions were pharmacokinetic interactions. The mechanisms of the remaining 8 (4.0%) interactions were unknown. CONCLUSION: ADRs and DDIs occurred in patients with cardiovascular diseases receiving pharmacological treatment. Respiratory, gastrointestinal and central nervous systems were the commonest systems affected by ADRs. Manifestation of ADR was directly related to the number of co-morbidities and age of patients.

Keywords

Ghana, Adverse Drug Reactions, Drug Interactions, Heart Failure, Ischaemic Heart Disease, Arrhythmias

1. Introduction

Cardiovascular diseases (CVDs) are associated with immerse reduction in quality of life, numerous hospitalizations and huge financial burden on patients. Many pharmacological agents are usually combined to manage inflammation, haemodynamic and neurohormonal alterations which occur in patients with CVDs. Combination therapy is however challenged with the possibility of undesired drug interactions and adverse effects. Clinical trials, cohort studies and post marketing surveillance over the years have been of immerse use in detecting risk profiles of medicines encountered during research or reported by patients after drug utilization [1-2].

According to WHO, an adverse drug reaction (ADR) is defined as a drug response which is noxious and unintended, and occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function [3]. Ranked as the fourth leading cause of death in the United States, ADRs have resulted in detrimental effects such as congenital anomalies, hospitalizations, disabilities and death [4]. Though not all adverse effects are fatal, ADRs limit the use or lead to drug withdrawal from market [5].

A drug-drug interaction (DDI) refers to the tendency of a drug to have its effects modified by the presence of another (pharmacodynamic effects) or altered pharmacokinetics [6]. These interactions may elevate or diminish efficacy, induce toxicities or treatment failure of drugs. There is a direct relationship between the number of prescribed drugs and the number of interactions that can occur in an individual. Some factors which increase the incidence of DDIs include severity of patient condition, multiplicity of conditions, age, organ function of individual, and the dose of administered drug [7].

Data on drug related problems linked with prescribed drugs for cardiovascular patients in sub-Saharan Africa is limited. As such, this study was designed to determine the DDIs and ADRs that occurred in patients with CVDs receiving pharmacological treatment at the cardiac clinic, Komfo Anokye Teaching Hospital (KATH), Kumasi, Ghana. The study also evaluated the interventions which were provided to counteract the effects of DDIs and ADRs.

2. Method

2.1. Study Design

The design of the study was cross-sectional and carried out at the outpatient cardiac clinic, Directorate of Medicine, KATH, Ghana from January 2015-June 2015. Ethical approval was obtained from the appropriate ethical committee, and each study participant signed an informed consent.

2.2. Study Population

Two hundred and forty-eight (248) patients were recruited for the study. The sample was drawn from a population of patients attending outpatient cardiac clinic with the confirmed diagnosis of the CVDs of interest and are being managed with pharmacological agents. Eligible participants were newly or previously diagnosed patients with heart failure, ischaemic heart disease or arrhythmias aged 13 years and above who were not receiving treatment for life threatening diseases such as cancer. Patients who were unconscious and critically ill requiring immediate hospital admission, and those who refused to give consent for the study were excluded.

3. Data Collection

3.1. Recruitment

Eligible patients were identified by clinicians of the research team as they made their routine attendance to the hospital. Only individuals who were undergoing treatment and are being managed with medications were purposively sampled, interviewed, and data collected using a data collecting form.

3.2. Adverse Drug Reactions Report

Adverse drug report involved documentation of adverse effects to previous cardiovascular therapy. ADRs were categorized based on the type of ADR, organ or system implicated, suspected medicine (s) that induced the effect and intervention provided to avert the problem.

3.3. Drug Interactions Report

All medications prescribed during routine visit were also documented to assess for DDI. The prescription per patient was entered into an online medical information source (Medscape) to generate the interactions. The interactions were compared to Stockley's drug interaction, 9th edition (2010) and British National Formulary, 66th edition (2013/2014). DDIs were categorized based on type of interaction as: pharmacodynamic interactions (these produced synergistic or additive, antagonistic or opposing effects), pharmacokinetic interactions (these affected absorption, distribution, metabolism and excretion of medicines) or unknown. The interactions were also classified based on the gravity (severe, significant or mild).

3.4. Data Analysis

Completed data collection forms were screened to ascertain validity of data and transferred unto computer spreadsheet (Microsoft Excel, 2013). Subsequently, data was analyzed with SPSS statistics for windows, version 22, Armonk, NY: IBM Corp. Simple averages and their corresponding standard deviations were used to summarize

the quantitative data (continuous) whereas proportions were used to summarize categorical data. Drug interactions and adverse effects were presented in respective proportions or numbers. Also, graphs and other charts were used were necessary to present some of the results using Microsoft Excel version 15.

4. Result

4.1. Demography

Out of the 248 patients, 56.4% were females and 43.6% males. The age range for participants was from 13 – 105 years. The average age was 60 years with a standard deviation of 17.9 (60 years ± 17.9). Mean age for women was less than that of men (Women: 59.1 ± 18.4; Men: 62.0 ± 16.8).

4.2. Adverse Drug Reactions

A total of 19 adverse reactions were reported in 17 patients, that is 6.9% of the sample. Two people experienced 2 ADRs each, with the remaining patients reporting 1 ADR each. The proportion of these ADRs were 17.6%, 35.3% and 49.1% for age ranges 30-49, 50-69 and 70-89 years and the average age occurred at 65.2 years. More men reported ADRs with the ratio of men to women being 0.59:0.41.

When an assessment was made regarding adverse events to number of prescribed medicines and co-morbidities, it showed that the average patient reporting an adverse effect suffered from 2.8 (~3) co-morbidities and was prescribed 6.3 (~ 6) medicines by their physicians.

The medical interventions provided for patients included withdrawal or replacement of suspected drug and provision of other drugs to counteract the adverse effect. Summary of the adverse effects of the pool of drugs administered to patients, and associated interventions provided to avert the ADRs are outlined in table 1.

Table 1. *Type of adverse effect, class, frequency and associated interventions.*

POSSIBLE ADVERSE EFFECT	SYSTEM CLASSIFI-CATION	SUSPECTED DRUG(S)	FREQUENCY	INTERVENTION(S)
Gastric pain	Gastro-intestinal System	Aspirin only Aspirin/arthrotec Spironolactone/bisoprolol Clopidogrel/ rosuvastatin/ Bisoprolol	6 1 1 1	Antacid Aspirin replaced with Clopidogrel Aspirin withdrawal Omeprazole + domperidone PPI (Omeprazole/Esomeprazole) No Intervention
Cough	Respiratory System	Lisinopril	5	Lisinopril replaced with Losartan
Headache	Central Nervous system	Amlodipine/ methyldopa	1	Nifedipine replaced with Amlodipine Opioid analgesic (Tramadol)
Erectile dysfunction	Central Nervous system	Losartan/bisoprolol	1	Phosphodiesterase type 5 inhibitor
Back pain	Musculo-skeletal system	Atorvastatin	1	NSAID (Celecoxib)
Hypotension	Central Nervous system	Lisinopril/ bisoprolol	1	Dose reduction of drugs

Note: PPI-Proton pump inhibitor
NSAID-Non-steroidal anti-inflammatory drug

4.3. Drug-Drug Interactions

The assessment of existing possible drug related problems and interaction for diseases which were assessed in this study employed 169 paired drugs that produced 202 interactions. Aspirin recorded the highest percentage interactions (21.3%, n=43), followed by furosemide (11.4%, n=23) and bisoprolol (12.4%, n=25) as showed in figure 1.

The interactions were further classified based on severity (mild, significant and severe) and type (pharmacokinetic and pharmacodynamic). Table 2 shows the interactions seen in this study. Out of the 202 interactions, 152 (75.2%) of the interactions were significant whereas 37 (18.3%) and 13 (6.4%) were mild and severe respectively. Again, 122 (60.4%) of the interactions were pharmacodynamic interactions whereas 72 (35.6%) of interactions were pharmacokinetic interactions. The mechanisms of the remaining 8 (4.0%) interactions were unknown. Table 2 shows the type and severity of interactions.

From the list in table 3, digoxin, lisinopril and carbamazepine were the commonest drugs involved in severe drug interactions. The associated risk factors and specific interaction of drugs involved in severe interactions are outlined in detail.

Two drug interactions that occurred were likely to have resulted in adverse effects in two patients; aspirin + diclofenac, and bisoprolol + lisinopril resulted in gastric pain and hypotension respectively. Actual incidence of adverse effect from interacting drugs was 0.1%. One intervention (clopidogrel and omeprazole) provided to address an adverse effect possibly undergoes DDI as well.

Table 2. *Drug-drug interactions classified per interaction type and severity.*

INTERACTION TYPE	NUMBER OF INTERACTIONS			
	MILD	SIGNIFICANT	SEVERE	TOTAL
Pharmacodynamic	6	111	5	122
Additive/Synergism	2	66	5	73
Antagonism	4	45	-	49
Pharmacokinetic	28	36	8	72
Absorption	3	3	3	9
Distribution	1	1	-	2
Metabolism	6	20	5	31
Excretion	18	12	-	30
C. Unknown Mechanism	3	5	-	8
Total	37	152	13	202

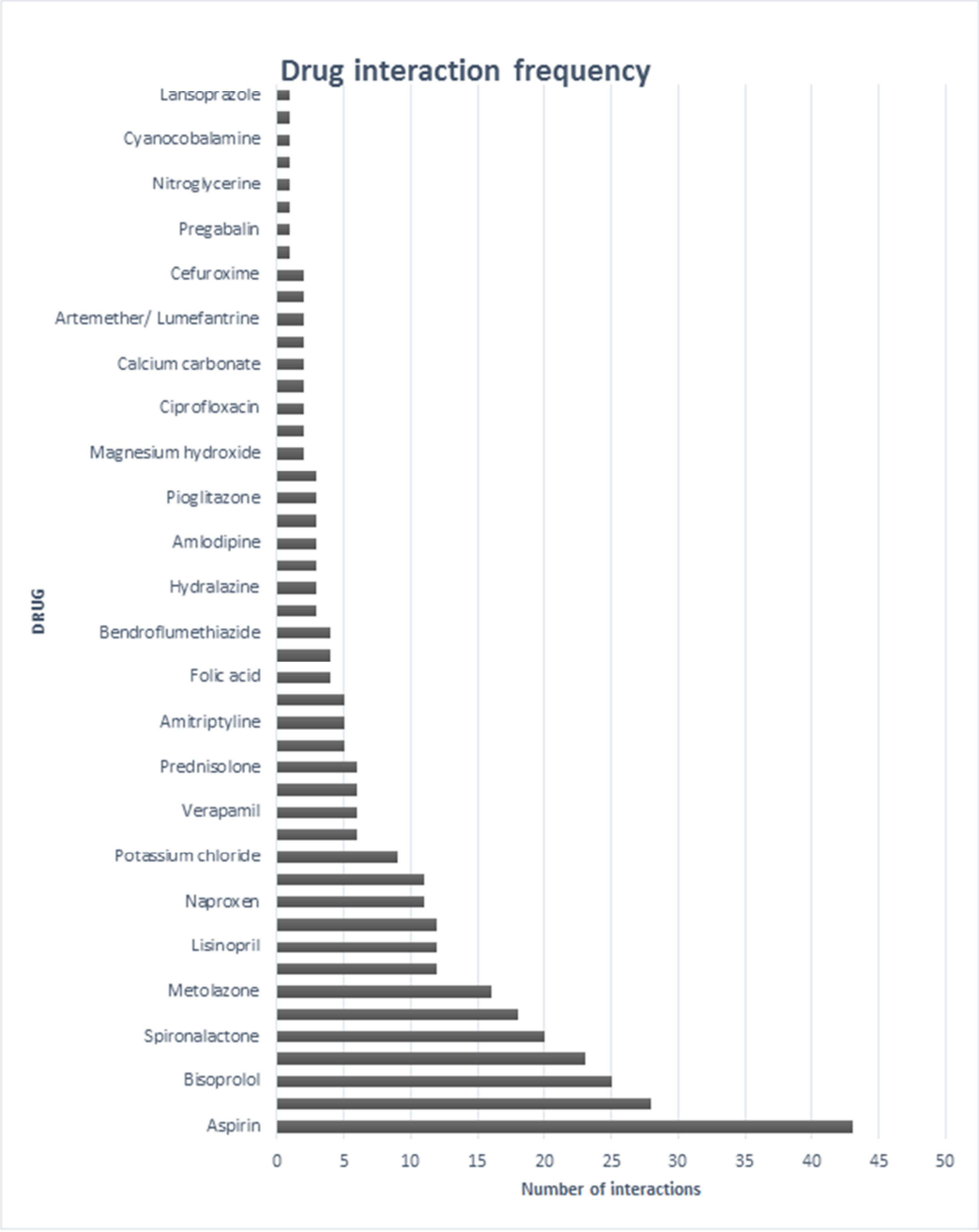

Figure 1. *Frequency of individual drugs in drug-drug interactions.*

Table 3. *List of severe drug-drug interactions which were generated from online medical information in Medscape using patients' medication data..*

DRUG INTERACTION	EFFECT/ MECHANISM	RISK
Lisinopril+Potassium chloride	Additive potassium retaining effects	Hyperkalemia
Lisinopril +Pregabalin	Pharmacodynamic synergism	Angioedema
Lisinopril + Losartan	Pharmacodynamic synergism	Hyperkalemia
Bisoprolol +Verapamil	Both increase antihypertensive blocking effect	Bradycardia
Spironolactone+Potassium chloride	Both increase serum potassium	Hyperkalemia
Carbamazepine +Atorvastatin	Carbamazepine decreases atorvastatin by affecting hepatic/intestinal enzyme CYP3A4 metabolism	
Carbamazepine+Esomeprazole	Carbamazepine increases esomeprazole by affecting hepatic/intestinal enzyme CYP3A4 metabolism	
Carbamazepine + Clopidogrel	Carbamazepine decreases clopidogrel by affecting hepatic/ intestinal enzyme CYP 2C9/10 metabolism	Thromboembolism
Omeprazole + Digoxin	Omeprazole increases digoxin by increasing gastric pH	Digoxin toxicity
Omeprazole + Clopidogrel	Omeprazole decreases clopidogrel by affecting hepatic/ intestinal enzyme CYP2C9 metabolism	Thromboembolism
Aluminium hydroxide + Digoxin	Aluminum hydroxide increases digoxin by increasing gastric pH	Digoxin toxicity
Esomeprazole + Clopidogrel	Esomeprazole decreases clopidogrel by affecting hepatic enzyme CYP2C19 metabolism.	Thromboembolism
Esomeprazole + Digoxin	Esomeprazole increases digoxin by increasing gastric pH.	Hypomagnese-mia/ Digoxin toxicity

5. Discussion

Consistent with reports from Singhal *et al*., the current study indicate that most frequent ADRs per system classification were related to the gastrointestinal, respiratory and central nervous systems [8]. Gurwitz *et al*. also observed that about 25% of cardiovascular medications resulted in ADRs [9]. This therefore shows that cardiovascular medications induce appreciable number of ADRs. Appropriate interventions for patients which include drug withdrawal, dose adjustment and alternative drugs administration could possibly have reduced the risk of patient non-compliance to therapy and its untoward cardiovascular implications.

From this study, ADRs appeared to be more common in males than females though a number of studies support the hypothesis that female gender is a risk factor for ADR incidence. Different results have been obtained in other studies. Whilst Singhal *et al.* indicated a higher incidence of ADRs in men (62.1%) compared to women, Kaur *et al.* observed that women had increased inclinations to develop ADRs [8, 10]. The attributable reasons for increased ADRs in women include lean body mass, higher percentage of adipose tissue, higher volume of distribution, reduced conjugation and glomerular filtration rate as well as differences in pharmacodynamic effect. Increased activity of cytochrome P450 3A4 isoenzyme in women enhances drug metabolism and also induces ADRs from active metabolites. In addition, some drugs are known to be more efficient in women and these are also associated with greater ADRs. Administration of gender specific drugs for conditions like menstruation, pregnancy and birth control and menopause may account for ADRs as well [11].

Age is a known risk factor for ADRs. In this study, the average age at which ADR occurred was 65.2 years. This is similar to the mean age of 61 years by Kaur *et al.* [10]. Out of the 17 people that reported with ADRs, ADR occurrence was noted to increase with age and 62.5% of cases occurred in patients above 60 years. Older patients experience higher rate of ADRs as a result of pharmacodynamic and pharmacokinetic changes, increased co-morbidities, compromised organ function and increased intake of medicines.

An average of 6 medicines and 3 co-morbidities were associated with the patients reporting with ADRs. Many studies also confirm polypharmacy and multiple co-morbidities to play vital role in inducing ADRs and incidence of DDIs. Baxter *et al*. reported that the incidence of potential DDIs is about 40% (3 medicines) and 80% (7 or more medicines) [7]. In this study, only 0.1% of DDIs resulted in adverse effects and this is consistent with several reports that DDI incidence is very minimal. They are however worth investigating as some DDIs could be life threatening to the patient.

Some causes of ADRs and DDIs to include patient non adherence to therapy, complex medication regimen, wrong doses, inadequate laboratory monitoring of medicines (e.g. warfarin and digoxin), dispensing errors, self- medication with left over medicines or over the counter medicines, inadequate provision of information on medication by healthcare providers and refusal of patients to stop taking medicines despite instructions from physician to discontinue therapy [9-10].

Pharmacovigilance units and drug information centres in hospitals which are vital information units must therefore be adequately resourced to educate the populace on ADRs and address reported ADRs appropriately. Early detection and documentation of adverse effects, monitoring and management of patients as well as patient education on inappropriate use of prescribed and over the counter medicines can avert undesired ADRs and ensure optimum benefit from prescribed interventions and also ensure safety.

6. Conclusion

Adverse drug effects and drug interactions occurred in patients with cardiovascular disease receiving pharmacological treatment for cardiovascular disorders.

Respiratory, gastrointestinal tract and central nervous systems were the commonest systems affected by the ADRs. Manifestation of ADR was directly related to the number of co-morbidities and age of patients.

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