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Adverse drug reactions report among hospitalized patients with hypertension in a Nigerian Tertiary Healthcare Centre: a retrospective study

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Abstract
Adverse drug reactions (ADRs) are serious clinical problem with growing global concern. This study focused on incidence and outcome of ADRs among in-patients with hypertension in Nigeria. This was a cross-sectional study on incidence of adverse drug reactions among in-patients with hypertension conducted in the University College Hospital (UCH), Ibadan, Nigeria, within June 2012 to May 2013. Of 196 patients, 105 (53.6%) were male, and 91 (46.4%) were female. Prevalence of ADRs was 53 (27.04%), of these, 28 (52.8%) were male, and 25 (47.2%) were female. Adverse drug reaction was cause of admission in 2 (1.02%) patients. Prevalence of ADRs during hospitalization was 51 (26.02%) patients. Patients with adverse drug event spent approximately additional 5 days more in bed compared to those without adverse drug reactions (p = 0.028). ADRs experienced by the patients were managed by withdrawing the suspected drug(s). In conclusion, ADR was cause of admission in 1% of in-patients with hypertension, while ADRs was recorded in 53 (27.04%) hospitalised patients with hypertension. Patients that experienced ADR spent additional approximately five days in hospital compared to those without adverse drug effect during hospitalization.

Keywords: Adverse drug reaction, hospitalized patients, incidence, hypertension, dechallenge

Introduction

Adverse drug reactions (ADRs) are serious clinical problem, and a growing concern of the health care systems. The World Health Organization (WHO) defined an adverse drug reaction as unpleasant and unintended response to drug which results from the use of given medications at a normal dosage during normal use. Adverse drug reaction in hospitalized patients can be separated into two categories; those that cause of admission of patients into hospital, and those that occur in patients after hospital admission [1]. A large prospective study has shown that ADRs were responsible for 6.5% of overall hospital admissions [2]. A meta-analysis suggested that in-hospital incidence of ADRs are within the fourth and sixth commonest cause of death in the United State [3]. From numerous studies, the percentage of patients experiencing an ADR during hospitalization varies. The diversity of the results of the prevalence of ADRs experienced by patients from different studies may be explained by the different definitions of ADRs, the patients target groups, and the methods by which ADRs were sought and detected [4]. Also, it had been estimated that patients who developed adverse effects during hospitalization spent about 1.2–3.8 days longer than patients who did not, with a substantial increase of healthcare costs [5].

Prevalence of hypertension increases globally. In fact, hypertension is the most common condition seen in primary health care [6]. It is important that blood pressure be minimize to a reasonable level in order to prevent cardiovascular diseases and organ damage in patients with hypertension. Lowering blood pressure often requires the use of two or more antihypertensive drug classes. However, most antihypertensive drugs are capable of producing adverse effect either when used individually, in combination or when used concomitantly with other drugs even at prescribed doses. Information on adverse drug reactions among hypertensive patients in Nigeria were often reported as part of drug utilization studies on patients visiting the outpatient clinics. There is paucity of information on incidence of ADR among hospitalized hypertensive patients. In addition, from previous studies, percentage of patients that experienced adverse drug reactions during hospitalization have been reported to range from 1.5 to 53% [7, 8]. These variation in prevalence of ADR may be influenced by means by which ADR were sought and detected. In this study, we report incidence of adverse drug reactions experienced among hospitalized patients with hypertension based using information from medical record.

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Materyal and Methods

Study design
This study is a retrospective, observational study to report incidence and prevalence of adverse drug reactions among in-patients with hypertension admitted into University College hospital, Ibadan within June 2012 to May 2013.

Study Location
The University College Hospital (UCH) is an 850-bedded hospital located in Ibadan, Oyo state, Nigeria.

Study population and questionnaire
A total of 198 patients' case notes were retrieved from medical record, they were selected using stratified random selection. Required information about the patients were filled into structured questionnaire. Section one contain socio-demographic information such as age, sex, occupation, marital status, ethnicity, and length of hospitalization. The second section was prescription data; drug used before hospitalization, when hospitalized with date of starting and terminating the drug, pre-existing medical conditions, co-morbid conditions, relevant tests/laboratory data, suspected adverse reaction, description of the reactions, onset/stop date of occurrence, and management of the ADR recorded by the physicians were documented. In the third section, laboratory reports on biochemical parameters of patients with date were recorded. Suspected adverse drug reactions were categorized based on causality [9] and severity [10].

Study Approval
Permission to carry out the study was approved by the Head, Department of medicine, University College Hospital (UCH), Ibadan. Confidentiality of the patients was thoroughly maintained throughout the study period.

Statistical analysis
The data were processed and presented using SPSS 22.0. Descriptive analyses were used for prevalence of parameters. Independent student t-test was used to compare differences in number of day spent between patients that experienced ADR and those without ADR (p <0.05). Chi-square and cross-tabulation analyses were used to asses association between categorical variables (p<0.05).

Results

In 196 patients, 105 (53.6%) were male, and 91 (46.4%) were female. Patients of middle age group 91 (46.4%), while the young and elderly patients population were 52 (26.5%) and 53 (27.1%) respectively. Majority of the patients 132 (67.3%) completed tertiary education. Further information on socio-demographic characteristics of the patients can be found in Table 1 below.

Fifty-three (27%) of the patients have incidence of adverse drug reaction. Of these, 28 (52.8%) were male, and 25 (47.2%) were female patients. Distribution of ADR observed in age groups were as follow; 24 (45.3%) in middle age (45-64 years old), 14 (26.4%) in elderly (≥65 years old), and 15 (28.3%) in the young (16-44 years old). ADR was cause of admission in 2 (1.02 %) patients. There was a case of Tegretol® (Carbamazepine) induced hypertension in a patient, and a case of paluther® (Arthemeter) aggravated tinnitus. Twenty-six (13.27%) among patients that experienced adverse drug reactions had early record of herbal use.

Table 1. Socio-demographic character of hospitalized patients with hypertension

Variables	Frequency (%)
Age	
16-44	52 (26.5)
45-64	91 (46.4)
≥65	53 (27.1)
Sex	
Females	91 (46.4)
Males	105 (53.6)
Marital status	
Single	13 (6.6)
Divorced	5 (2.6)
Married	141 (71.9)
Widow	37 (18.9)
Occupation	
Civil servants	32 (16.3)
Self employed	122 (62.3)
Unemployed/retiree	42 (21.4)
Religion	
Christian	112 (57.1)
Islam	84 (42.9)
Education	
Primary	12(6.1)
Secondary	52 (26.5)
Tertiary	132 (67.4)
Ethnicity	
Yoruba	171 (87.2)
Other tribes	25 (12.8)
Alcohol and Smoking	
Alcohol only	32 (16.3)
Smokes only	4 (2.0)
Alcohol and smoking	16 (8.2)
Non-alcoholic, non-smokers	144 (73.5)
BMI*	
Non obese	31 (15.8)
Overweight	55 (28.1)
Obese	110 (56.1)

*Body mass index classification was based on WHO, 1995 [11]

Prevalence of ADR during in hospital stay was 51 (26.02%), with a patients experiencing one, two or more ADR related symptom. Electrolyte imbalance was common incidence of ADR seen among hospitalized hypertensive patients. Increased serum urea was reported in some patients on Ramipril and Lisinopril, which were both angiotensin converting enzymes inhibitors (ACEIs). Adverse drug reactions were managed by withdrawing the causal drug (Dechallenge). Detailed information on incidence of ADR experienced among hospitalized hypertensive patients are on Table 2.

Table 2. Adverse drug reactions reported among in-patients with hypertension

ADR/Suspected cause	Frequency (%)	Suspected drug (s)	Severity	Management	Outcome
Cause of Admission					
Hypertension,	1 (0.51)	Tegretol®, Paluther®	Severe	Withdrawal of suspected drug	Hospitalized & discharge
Tinnitus	1 (0.51)		Severe		
On Admission					
Hyponatremia	7 (3.57%)	Furosemide, mannitol	moderate	Withdrawal of suspected drug	Prolong hospitalization & discharged
Hypernatremia	5 (2.55)	Normal saline	moderate	Withdrawal of suspected drug.	Prolong hospitalization & discharged
Hyperkalemia	7 (3.57)	ACEIs	moderate	Withdrawal of suspected drug	Prolong hospitalization & discharged
Hypokalemia	24 (12.25)	Furosemide, mannitol	moderate	Withdrawal of suspected drug	Prolong hospitalization & discharged
Hyperchlorinemia	2 (1.02)	Normal saline	moderate	Withdrawal of suspected drug	Prolong hospitalization & discharged
Increased serum urea	15 (7.65)	Ramipril, Lisinopril	moderate	Withdrawal of suspected drug	Prolong hospitalization & discharged

Discussion

Adverse drug reactions (ADR) cause considerable economic and life burden. Current study assessed the incidence of ADR among in-patients with hypertension in a Nigerian tertiary health care centre. From the result of the present study, there were few cases of ADR reported as cause of Admission, and higher incidence of ADR were reported during hospital stay.

ADR related symptoms are often managed at emergency or medical outpatients unit and patients can be discharged from there. Low Incidence of ADR as cause of hospital admission in our study correlates with early studies on incidence of adverse drug reactions among in-hospital patients [2,12].

Among ADR as cause of hospital admission reported was Carbamazepine (Tegretol®) related hypertension. Carbamazepine is used in treatment of neuropathic pain, affective disorders and epilepsy, its principal metabolite carbamazepine-10,11-epoxide has anticonvulsant activity [13. Karsarkis *et al* [14] have reported cardiac effects of **carbamazepine** where young patients experienced sinus tachycardia after **carbamazepine** over dosage, and older female patients with potentially life-threatening bradycardia or atrioventricular block associated with raised blood concentrations of **carbamazepine at therapeutic dose**. There was also a report of fatal syncope, probably due to ventricular asystole, in a 20-year-old patient [15]. Documented adverse effects of carbamazepine were rashes, oedema, arrythmias, heart failure, Steven Johnson syndrome, disturbance of cerebellar and ocular-motor function, incidence of haematological reaction which includes bone marrow suppression and reduced platelet count [16]. Hypertension aggravated from use of carbamazepine may result from any of the aforementioned cardiovascular and neurological related adverse effect of carbamazepine. Paluther, an artemisinin derivative, which is fast acting intramuscular schizonticidal antimalarial that inhibits the development of trophozoites and thus prevents progression of the disease have been reported to cause adverse effects like QT prolongation, tinnitus, neurological electrocardiography, and biochemical abnormalities [17]. These adverse effects may be the cause of hypertension seen in other patients admitted due to adverse reaction.

Prevalence of adverse drug reaction among hypertensive in-patients in this study (26.02%) was similar to that reported in HYVET retrospective study among hospitalized elderly hypertensive patients [18]. During hospitalization, hyponatremia and hypokalemia were the common adverse drug reactions experienced, these two electrolyte imbalance were mostly attributable to the combined use of furosemide (Lasix®) and IV mannitol, or the use of any of this drug. Beside the expected natriuresis produced by IV furosemide, a loop diuretics and mannitol, an osmotic diuretics, they may as well cause hypokalemia because they also facilitate potassium excretion. Acute renal failure has been documented in the infusion of I.V mannitol [19]. Fluid and electrolyte imbalance have been reported to be the most common effect of mannitol infusion [20]. Decrease in aldosterone secretion as a result of use of ACEIs leads to hyperkalemia [21]. Hyperkalemia were often seen in patients on ACEIs, however dietary supplements taken by some patients may also be contributing factor. In patients that experienced hyperchlorinemia and hypernatremia, normal saline is the suspected cause. However, hyperchlorinemia and could also be as a result of poly-pharmacy [22]. The suspected drugs attributable to those with increased serum urea were ACEIs. However, other conditions that may cause increased level of urea in blood could be increase catabolism, high protein diet or decreased glomerular filtration rate [23].

Length of hospitalization was significantly greater in patients that experienced ADR compared to those that were not. Patients that developed ADR on hospitalization requires intensive monitoring, withdrawal (dechallenge) or

adjustment of causal agents and eradication of ADR related symptoms. These are contributing factors which requires consideration when comparing between patients with ADR and those without ADR during hospitalization. In relation to this study, where patients with ADR spent additional average of five days on hospitalization, study by Rodrigue-Monguio *et al* [5] have suggested that patients who develop adverse drug reaction during hospitalization may spend an average of 1-4 days longer than those who were not.

Conclusion

Adverse drug reaction recorded among hospitalised hypertensive patients was 27%, ADR as cause of admission was seen in 0.01 % (one in hundred). Patients that experienced ADR spent approximately five additional days in hospital compared to those that did not.

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Authors' contribution
ADA and AMA designed the experiments; AMA performed the experiments; AMA analysed the data; AWA reviewed and corrected the work.

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