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Adverse drug reactions (ADRs) attributable to antihypertensive medicines constitute 3.15% of Individual Case Safety Reports (ICSR) received by the Nigerian National Pharmacovigilance Centre, through spontaneous reporting system across the country as at March, 2010. This issue discusses the reported ADRs attributable to antihypertensive medicines. Other features in this edition include; compilation of adverse drug reaction reports of interest as reported in "Reaction Weekly". Your comments and acknowledgement of receipt of this issue through our email would be most appreciated.

PHARMACOVIGILANCE OF ANTIHYPERTENSIVE MEDICINES

INTRODUCTION

Hypertension is an increasingly important medical and public health issue worldwide. Reliable information about the global prevalence of hypertension is essential to the development of national and international health policies for prevention and control of this condition. High blood pressure is estimated to have caused 7.6 million premature deaths (13.5% of the total) and contributed 92 million disability-adjusted life years

(DALYs) worldwide in 2001.[1] In the year 2000, nonoptimal blood pressure was estimated to have caused approximately 7.1 million deaths (12.8% of the total) and contributed 64.3 million DALYs.[2] According to a pooled data from different regions of the world to estimate the overall prevalence and absolute burden of hypertension in 2000, and to estimate the global burden in 2025, results showed that overall, 26·4% of the adult population in 2000 had hypertension and 29·2% were projected to have this condition by 2025. The estimated total number of adults with hypertension in 2000 was 972 million; 333 million in economically developed countries and 639 million in economically developing countries. The number of adults with hypertension in 2025 was predicted to increase by about 60% to a total of 1·56 billion. This result shows that prevention, detection, treatment, and control of this condition should receive high priority.[3]

In sub-Saharan Africa (SSA), the prevalence of cardiovascular disease and hypertension is increasing rapidly. The current prevalence in many developing countries, particularly in urban societies, is said to be already as

[1] Lopez AD, Mathers CD, Ezzati M, Jamison DT, Murray CJ. Measuring the Global Burden of Disease and risk Factors, 1990–2001. Global Burden of Disease and Risk Factors. 2006. Available at: http://www.dcp2.org/pubs/GBD. Accessed March 5, 2006.

[2] CM, Vander Hoorn S, Law MR, Elliott P, MacMahon S, Rodgers A. Blood pressure and the global burden of disease 2000. Part II: estimates of attributable burden. *J Hypertens.* 2006; 24: 423–430.[Medline] [Order article via Infotrieve] Lawes

[3] Patricia M Kearney MD a d, Megan Whelton BS a, Kristi Reynolds PhD a, Paul Muntner PhD a b c, Prof Paul K Whelton MD a b c, Prof, Dr Jiang He MD a b c. Global burden of hypertension: analysis of worldwide data. The Lancet, Volume 365, Issue 9455, Pages 217 - 223, 15 January 2005 doi:10.1016/S0140-6736(05)17741-1

high as those seen in developed countries. SSA is currently battling with communicable diseases such as malaria and HIV, and most governments in the region have limited resources and health budgets. An increasing burden of hypertension in this region is therefore likely to be of grave consequence because very few people will get treated and control is likely to be low. This in turn would result in high morbidity and mortality from potentially preventable complications such as stroke, myocardial infarction, and renal failure.

Many classes of antihypertensives have been used to lower blood pressure. Among the most important and most widely used are the thiazide diuretics, the ACE inhibitors, the calcium channel blockers, the beta blockers and the angiotensin II receptor antagonists. Which type of medication to use initially for hypertension has been the subject of several large studies and resulting national guidelines. The fundamental goal of treatment should be the prevention of the important endpoints of hypertension, such as heart attack, stroke and heart failure. The several classes of antihypertensives also differ in side effects profiles, ability to prevent endpoints and cost. The choice of more expensive agents, where cheaper ones would be equally effective may have negative impacts on national healthcare budgets.

It is imperative that the safe use of antihypertensives is monitored during treatment to ensure that hypertensive patients are not over burdened with other adverse reactions due to the drugs. Studies conducted in developed countries have consistently shown that approximately 5% of hospital patients are admitted into hospital as a result of an ADR, while 6-10% of in-patients will experience a serious ADR during hospitalization.

The percentage of hospital admissions due to ADRs in some countries is about or more than 10%, e.g. **Norway 11.5%, France 13.0%, UK 16.0%.** Adverse Drug Reactions (ADRs) are either possibly or definitely avoidable. Access to medicines we know is a human right, but preventing avoidable harm from the use of those medicines is a professional and moral obligation of healthcare practitioners. Although the occurrence of some of these reactions is not predictable, sufficient knowledge of the conditions under which they are likely to occur may help prevent their occurrence. It therefore becomes expedient for health practitioners to rise up to the demands of their profession and protect their patients.

So many kinds of adverse drug reactions associated with the use of antihypertensives have been reported to the National Pharmacovigilance Centre. This publication will try to x-ray the individual case reports in order to categorize and identify the frequency of reported ADRs attributed to antihypertensives.

SUSPECTED ANTIHYPERTENSIVE INDUCED ADVERSE DRUG REACTIONS REPORTED TO THE NATIONAL PHARMACOVIGILANCE CENTRE, NAFDAC, ABUJA

A REVIEW OF ADRs ON THE NPC DATABASE BY PHARMACOLOGICAL CLASS

DRUG CLASS	NO. OF REPORTS
ANTIRETROVIRALS	1438
ANTIMALARIAL	327
ANALGESIC	217
ANTIBIOTIC	202
ANTIHYPERTENSIVE	74
ANTIDIABETIC	17
ANTI TB	23
ANTIASTHMATIC	12
ANTIEMETIC	10
ANTIPSYCHOTIC	21
BIOLOGICALS	10
HEMATINIC	10
HERBAL	22
UNCLASSIFIED	126
TOTAL	2509

Fig. 1:

Table 1

SUMMARY OF ADRs DUE TO ANTIHYPERTENSIVES IN THE NPC DATABASE			
SUSP_DRUG	**FREQUENCY**	**AGGREGATE ADR**	**OUTCOME/REMARKS**
Amlodipine	5	Frequent micturition; Headache, swollen cheek, insomnia, feeling of uneasiness and hotness within the body.	All Resolved
Captopril	4	Internal heat, Headaches; Retrosternal pains, pains and feeling of restlessness in the Legs; Persistent dry cough; Abdominal pain, Vomiting	1 Unknown; 3 Resolved.
Lisinopril	16	Dry irritating cough; Hypotension; Generalized Urticaria; severe stomach pain; Generalized body rashes with eruptions in the mouth, difficulty in breathing , unilateral/ bilateral nasal obstruction, blurring of vision	4 Unknown; others resolved.
Spironolactone	3	GIT upset, Choking sensation, nausea; Palpitation.	All resolved; Dose was reduced in one case.
Frusemide	12	Nose bleeding; Poor Vision, darkness in eyes, Restlesness; increased BP 260/130mmHg, Restlesness, urticaria rashes, profuse sweating, Breathlessness; Pain around the nipples associated with swelling around the areolar; Lack of effectiveness; vomiting, sweating, weakness & hallucination.	1Death; 4 Unknown and 7Resolved

Nifedipine	17	Frequency of urination when drug is taken at night; Recurrent Orbital swelling and redness of the eyes 30-60 mins after digestion; Abdominal pain, noise and stool with mucus; Headache and Chest pain; Hotness of the body; Generalized Pruritis; Swollen of leg and Generalized weakness of the body; Dyspepsia, Indigestion, Belching after drug use; Dizziness, Tremor, Blurred vision, Postural Hypotension.	All but one resolved.
Ramipril	4	Persistent cough especially at night which lead to pains in chest, palpitations and headache; Swollen lip, Swollen face, Blurring of vision.	All Resolved.
Propanolol (Inderal)	1	severe itching of the body with swelling and reddish spot developed into dry spots	Ongoing as at the time of report
Amiloride / Hydrochlothiazide	6	Skin rashes with severe pruritus; Difficulty in swallowing, Dypsnea, Extreme weakness, Effort intolerance, Lethargy; Excessive micturition, Extreme weakness; Headache, swollen cheek, insomnia, feeling of uneasiness and hotness within the body.	1 Unknown; Others Resolved.
Methyldopa	2	Low mood, Light headedness, Dizziness and Poor sleep; Bilateral leg swelling, fatigue and dyspepsia	All Resolved

Brinerdin	2	Early morning abdominal congestion and discomfort; Wheeze, Chest tightness.	All Resolved.
Atenolol	2	Insomnia; Irregular heart beat (low heart beat rate< 50)	All Resolved.

SUBCLASS OF ANTIHYPERTENSIVES	NO. of Reports	PREVALENCE BY GEO-POLICAL ZONE						
		SS	SW	SE	NC	NE	NW	UNKNOWN
ACE Inhibitors	25	15	6	0	2	1	1	
Calcium Channel Blockers	21	12	5	0	2	1	1	
Diuretics	20	8	1	0	10		1	
Vasodilators	0	0	0	0	0			
Sympatholytic Agents	4	2	2	0	0			
Adrenergic Blockers	1	0	0	0	1			
Central Sympatholytic	0	0	0	0	0			
Unassessible	3	0	0	0	0			3
AGGREGATE ADR:	**74**	**37**	**14**	**0**	**15**	**2**	**3**	**3**

Fig. 2: Analysis of the ADRs due to Antihypertensive

ADVERSE DRUG REACTION CASE REPORTS CULLED FROM THE REACTIONS WEEKLY INVOLVING COMMONLY USED DRUGS IN NIGERIA

Calcium/ceftriaxone interaction

Severe cardiopulmonary adverse events in infants: 3 case reports.

Three infants developed severe cardiopulmonary adverse events during concomitants treatment with ceftriaxone and calcium containing products [dosage not stated in all case]. Two infants died.

A 50-day- old male infant, who was born at 30 weeks' gestation, presented with a urinary tract infection due to Klebsiella pneumonia. IV ceftriaxone 50 mg/kg as a 2- minute push was administered along with gentamicin and calcium-containing hyperalimentation. Ten minutes post injection, he developed shock, bradycardia and apnoea. He was successfully resuscitated. However, he experienced a similar episode 10 minutes after receiving a second dose on the following day. A ceftriaxone/calcium precipitate was considered as a possible cause, as well as anaphylaxis; the infant's mother had received ceftriaxone during pregnancy.

Three weeks after starting treatment with ceftriaxone for fever of unknown origin, a 3 week –old neonate died [sex not stated]. The patient was receiving concomitant IV calcium gluconate. Cardiomyopathy and deposition of crystals in the lungs were evident on autopsy.

An infant born at 35 weeks' gestation [sex not stated] received IV ceftriaxone 200 mg/day for maternal aminionitis, as well as an intravenous infusion of 10% calcium gluconate. A white precipitate was observed in the IV tubing. Around 2 hours after ceftriaxone administration, the patient developed pulmonary embolism and died. An autopsy revealed a white precipitate.

These 3 cases were among 7 reports received by the US FDA regarding severe cardiopulmonary adverse events associated with concomitant use of ceftriaxone and calcium-containing products. Five of the 7 cases involved premature infants. In all 7 cases the patients received IV calcium (calcium gluconate in 6 cases) and in 6 cases the ceftriaxone dosage ranged from 80 to 200 mg/kg/day. Six patients died. Autopsy were performed in 5 cases and crystalline material or white precipitate in the heart, lungs, kidneys and liver were noted in 4 cases.

Reference

Intravenous ceftriaxone (marketed as Rocephine and generics) and calcium drug- drug interaction: potential risk for cardiopulmonary adverse events in neonates. FDA Drug Safety Newsletter 2:24-25, NO. 3, 2009-USA

Carbamazepine/Opoid analgesics

Interaction leading to fatal carbamazepine poisoning, and fatal hydromorphone overdose, due to medication error: 2 Case reports.

Two patients died as a result of medication error: one from fatal carbamazepine poisoning following an interaction with dextropropoxypene-napsilate/paracetamol [acetaminophen], and one following inadvertent overdosing with hydromorphone.

An elderly man [age not stated] had been receiving carbamazepine 1g daily for many years for seizures [duration of therapy not stated], when he was hospitalized for repair of a hernia. His chart noted an "allergy" to codeine, despite the fact that the drug simply made him drowsy. Instead, he was discharged on oral dextropropoxyphene-napsilate/paracetamol [Darvocet-N; dosage not stated] for postoperative pain. After taking one dose the next day, he did not feel well. A day later, he was found dead in his home. A postmortem revealed a carbamazepine concentration of 22 Ug/mL (usual concentration 6-9 Ug/mL). His death was attributed to an interaction between dextropropoxyphene-napsilate and carbamazepine, increasing the serum concentration of the latter and leading to carbamazepine poisoning.

A 40-year-old man presented to the emergency department with severe throat pain. He had rarely received opiates prior to this, but his wife mentioned that he had previously failed to tolerate hydrocodone/paracetamol. For this reason, his doctor alternatively prescribed hydromorphone[Dilaudid]

for analgesia. At approximately 8am, he received IV hydromorphone 2mg. He was subsequently administered two further IV 2mg doses before 5pm, while in the nursing unit. He went into respiratory arrest [time to reaction onset not stated]. Despite resuscitation, he experienced permanent CNS impairment, and died. His death was reportedly attributed to an improper dose of hydromorphone.

Author Comment: "At times an allergy listing can mislead practitioners and cause unnecessary modification of treatment decision."

Cohen MR. True allergy or other symptoms? Too much hydrophone; patient safety increased in obstetrics; medication patch slips into incorrect automated dispensing cabinet pocket; volume control set safety. Hospital pharmacy 44: 654-656, No. 8, Aug 2009- USA

Ceftriaxone

Haemolytic anaemia in a child: case report.

A 6- year old girl developed haemolytic anaemia during ceftriaxone therapy for purulent meningitis.

The girl presented with a 3- day history of fever and vomiting. Purulent meningitis was diagnosed and she received dexamethasone and Ceftriaxone 100mg/kg/day. Her fever resolved on the fourth day and dexamethasone was discontinued. However, her fever recurred on the tenth day of treatment. A second CSF sample showed leucocytes with 20 polymorphic nuclei and 30 lymphocytes, with 64mg/dL protein, 66

mg/dL glucose and 122 mmol/L chloride, with a simultaneous blood glucose level of 123mg/dL. Suspecting a ceftriaxone-resistant pnuemococcal infection, vancomycin was added to cefriaxone. On the second day of this regime, she developed periorbital oedema and an urticaria- like rash right after the antibacterials were administered. Vancomycin was discontinued and replaced tiecoplanin. On the second day of this new regime, 15 minutes after she received ceftriaxone, she experienced acute tremors, tachypnea, vomiting, pallor and back pain. Her blood pressure was 70/40mm Hg, heart rate was 120/min and respiratory rate was 35/min. She received prednisolone and epinephrine [adrenalin]. Her haemoglobin level at this time was 4.3 g/dL, with 1% reticulocytes. She had an LDH level of 1346 U/L, a total bilirubin level of 11.8g/dL, a direct bilirubin level of 2.9g/dL and a haptoglobin level of 13.9 mg/dL. She had +2 urobilinogen and a positive direct coombs test. Her peripheral blood film showed collapsed erythrocytes.

Ceftriaxone was discontinued and the girl received isotonic saline with 5% dextrose, methylprednisolone and an erythrocyte suspension. Her haemoglobin levels began to recover on the third day of steroid treatment. She received methylprednisolone and teicoplanin for a total of 10 days. Post- discharge follow-up laboratory parameters were normal.

Doneray H, et al. Ceftriaxone-induced hemolytic anaemia: [Turkish}. Cocuk Sagligi ve Hastalikkari Dergisi 52: 154-158, No. 3, 2009 [Turkish; summarized from a translation]-Turkey

Metronidazole

Cerebellar syndrome: 2 case reports

Two patients developed cerebellar syndrome during treatment with metronidazole.

A 54- year-old man started receiving oral metrindazole [dosage not stated] for bronchiectasis. Two months later, he presented with an unsteady gait following a generalized tonic-clonic seizure, and a 3-day history of difficulty speaking. The estimated cumulative dose of metronidazole was about 60g. Bilateral cerebellar dysarthria and ataxia, and gait ataxia were observed on neurological examination. Over the next 4 days, his symptoms improved. One week later, his ataxia and dysarthria worsened, and he was hospitalized. MRI scan revealed bilateral symmetric hyperintensities in the dentate nuclei of his cerebellum. He had a second seizure after 1 month of admission, and phenytoin was started. He continued metronidazole for about 2 month after his initial presentation. At last follow-up, about 3 months after stopping metronidazole, his cerebellar syndrome had resolved; repeat MRI scan demonstrated complete resolution of his cerebellar lesions.

A 72-year old woman commenced metronidazole 500mg twice daily for an abdominal abscess. She developed cerebellar syndrome about 3 weeks later. Gait ataxia, and cerebellar dysarthria and ataxia were evident. Bilateral signal changes in her cerebellar dentate nuclei were observed on an MRI scan about 2 months later. Metronidazole toxicity was suspected, and metronidazole was withdrawn. Over the next few

weeks, her symptoms gradually resolved. Complete resolution of her cerebellar dentate lesions was seen on a follow- up MRI scan 1 month after metronidazole withdrawal. Two months later, she died of unrelated causes.

Author Comment: "The MRI changes . . . resolved in both patients, thereby implicating [metronidazole] as the causative agent."

Sarna JR, et al. Cases: Reversible cerebellar syndrome caused by metronidazole. CMAJ: Canadian Medical Association Journal 181: 611-3, No. 9, 27 Oct 2009 Canada

Haloperidol/olanzapine

Fatal pulmonary embolism in a physically restrained elderly patient: case report

A 68- year- old woman experienced a fatal pulmonary embolism during treatment with haloperidol and olanzapine and while being physically restrained.

The woman was admitted with a relapse of paranoid schizophrenia. On days 1 and 2, she received olanzapine 15mg and lorazepam. On days 2/3, she had severe delusions of being poisoned and refused to eat or drink. She also developed psychomotor agitation with violent behaviour and required restraint (9 hour on days 3) and compulsive medication. Her medications on day 3 included olanzapine 15mg, haloperidol 5mg and lorazepam. On day 4, she received olanzapine 15mg and lorezapam and, on day 5,

she received olanzapine 20mg, haloperidol 9mg and lorazepam. On day 6, she experienced a similar violent episode and she required 13.5 hours of restraint; medications on day 6 were olanzapine 20mg, haloperidol 13mg and lorazepam in addition to compulsive treatment. During that night, she had syncope for< 30 second with apnoea and oxygen desaturation (<75%). Following this, she was uncooperative and would not accept vital parameter control. Seven hours later, she experienced heart arrest and despite CPR, she died. Medication on day 7, included olanzapine 20mg, haloperidol 15mg and lorazepam. She had been physically restraint for 5 hours; the death occurred while she was being restrained. Autopsy findings concluded that the cause of death was an embolus causing complete obstruction of the trunk and left and right pulmonary artery branches. Consecutive acute right heart failure and dilatation of the right heart and marked venous congestion were also observed. Additional findings were slight generalized arteriosclerosis and slight left ventricular hypertrophy. Brain examination revealed a weight of 1310g, a small encephalomalacia in the right insular cortex, marked media calcification in the pallidum and atrophy.

Author Comment: "As our patient had no history or other risk factors for [venous thromboembolism]... We conclude that antipsychotic treatment in combination with physical restraint was the main etiologic factor for the fatal outcome in the case."

Hewer W, et al. Fatal pulmonary embolism following antipsychotic treatment and physical restraint. Phamacopsychiatric 42: 206-208, No. 5, Sep 2009. Available from: URL: hppt://dx.dio.org/10.1055/s-0029-1220932-Germany

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PLOT 2032 OLUSEGUN OBASANJO WAY, WUSE ZONE 7, ABUJA, PMB 5032 Wuse Abuja

Telephone: +2348033154512

E-mail: nafdac_npc@yahoo.com

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