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In this issue we present to you the summary of spontaneous adverse drug reactions (ADR) reports received on antibiotics usage across the country from September 2004 to 31st March 2008.
A total of six hundred and sixty(660) ADR reports were received in the period under review, out of which ninety- four (14.24%) were ADRs arising from antibiotic use ,thereby making them the drug class with second highest frequency in ADRs after antimarials in the database.

Table 1 shows the number of ADRs received on the various antibiotics- classes and their percentages as it relates to the total number of ADRs due to antibiotics in the database.
Table 2 however gives a further description of these ADRs, the type of antibiotics used, the frequency of occurrence, the final outcome after the adverse drug reaction was reported and further remarks on these case reports.

Table 1: SUMMARY OF ADR ON THE NPC DATABASE (SPECIAL ATTENTION ON ANTIBIOTICS)

S/N	ADRS ACCORDING TO ANTIBIOTIC CLASS	FREQUENCY	PERCENTAGE
1	QUINOLONES	24	(25.53%)
2	PENICILLINS	21	(22.34%)
3	SULFONAMIDES	20	(21.28%)
4	CEPHALOSPORINS	11	(11.70%)
5	MACROLIDES	11	(11.70%)
6	AMINOGLIGOSIDES	4	(4.26%)
7	CHLORAMPHENICOL	2	(2.13%)
8	TETRACYCLINES	1	(1.06%)

A DESCRIPTION OF ADRS ON THE NPC DATABASE THAT ARE DUE TO ANTIBIOTICS

S/N	CLASS OF ANTIBIOTICS	TYPE OF ANTIBIOTICS	FREQUENCY	REPORTED ADVERSE DRUG REACTIONS (ADRs)	OUTCOME	REMARKS
1	**QUINOLONES**	a. Pefloxacin b. Ciprofloxacin c. Levofloxacin d. Lomefloxacin **TOTAL**	9 12 2 1 **24**	Nausea. Vomiting, Abdominal discomfort, Headache, Dizziness, Muscle twitching, Fatigue, Fainting spell, Rashes, Numbness in the limb, Blisters on the lips and Loss of appetite.	Hospitalized: 1 Unknown: 5 Resolved: 14 Others: 1[∞]	[∞]Eruption of the skin was still visible at the time of report
2	**SULFONAMIDES**	a. Cotrimoxazole (Sulphamethoxazole + Trimethoprim)	**20**	Urticarial rash, Pruritis, Angiodema hypertemia, fever and mainly Steven's Johnson Syndrome (SJS).	Death: 3[®] Hospitalized: 5 Resolved with disability: 1 On going: 1 Unknown: 3 Resolved: 7	[®] The three death cases resulted from SJS involving a 2-year old baby, a 26-year old female and a 40-year old male patients.
3	**PENICILLINS**	a. Ampicillin b. Ampicillin + Cloxacillin c. Amoxicillin d. Amoxicillin + Clavulanic acid e. Flucloxacillin	1 6 2 9	Ear ache, Headache, fever, breathlessness, tachycardia, cardiac arrest, Generalized urticarial rashes, hyperpigmentated macular rash, Redness of eyes, Palpitation, sweating and headache, inflamed tongue, sore throat, swollen lips and High blood pressure	Death: 3[®] Hospitalized: 2 Resolved with disability: 1 On going: 1 Unknown: 4 Resolved: 9	[®] The death cases involved a 40-year old female who took both ampiclox and herbal preparation; a 52-year old man who died of cardiac arrest following a 1000mg of iv inj ampiclox and a 26-year

		f. Procaine-penicillin **TOTAL**	1 1 **21**			old female whose first reaction was body rash and subsequent death after 1.2g of Amoxicillin was administered.
4	**CEPHALOSPORINS**	a. Ceftriazone b. Cefuroxime c. Cephalexine d. Ceftazidime e. Cefotaxime **TOTAL**	4 2 2 1 1 **11**	Diarrhea, rigor, chills, hyperthermia, vomiting, restlessness, tachycardia, hyper pigmentation and fatal anaphylaxis.	Death: 1[e] Hospitalized: 2 Resolved with disability: 1 Unknown: 2 Resolved: 4	[e] A male patient who died of fatal anaphylactic shock following 200 mg of Ceftriaxone
5	**MACROLIDES**	a. Erythromycin b. Roxithromycin c. Clarithromycin **TOTAL**	6 2 1 **11**	Headache; Nausea; Pain; Malaise; severe GIT upset; Severe body itching and rashes and anaphylaxis.	Unknown: 5 Resolved: 4	No serious ADRs reported.
6	**AMINGLYCOSIDES**	a. Gentamycin b. Spectinomycin **TOTAL**	3 1 **4**	Nephrotoxicity, loss of consciousness, severe rashes and itching, dark patches and scaling.	Hospitalized: 2 Unknown: 2	
7	**CHLORAMPHENICOLS**	Chloramphenicol	**2**	Extra-pyramidal symptom; bleeding per rectum; abdominal pain	Hospitalized: 1 Resolved: 1	
8	**TETRACYCLINES**	Doxycycline	**1**	Feeling Uncomfortable, turning of stomach, dizziness	Resolved	
9	**Others**		**2**	Tingling sensation at infection site, palms, tightness of chest, constriction of throat and Steven Johnson Syndrome.	Hospitalized: 1 Resolved: 1	These are cases of polypharmacy with two or more classes of antibiotics.

ANTIBIOTICS AND MECHANISMS OF ADVERSE DRUG REACTIONS

Numerous mechanisms have been implicated in adverse reactions to drugs. These mechanisms however have not been fully understood, which may explain the difficulties in differentiating drug allergy from other forms of drug reactions by health professionals. A better comprehension of these mechanisms will help immensely in assessing the incidence of adverse drug reactions, evaluating risk factors, and defining management strategies[1].
Adverse events attributed to antibiotics are usually caused by three mechanisms:

1) Exaggerated response to the known pharmacological effects of the drug.
2) Immunologic reactions to the drug or its metabolites
3) Toxic effects of the compound or its metabolites[2].

Most antibiotic-related adverse events are precipitated by an extension of the drug's normal pharmacology and are often avoided by appropriate dosage adjustment.

Common Antibiotic-Related Adverse Reactions

Virtually all antibiotics have been associated with *C difficile*-related diarrhea and colitis. Ampicillin, clindamycin (Cleocin), and the cephalosporins are most commonly implicated. Presumably, these antibiotics render the intestinal tract permissive to the replication of vegetative forms of *C difficile* with concomitant elaboration of the A toxin, which is responsible for diarrhea and colonic inflammation. Rarely, if ever, have parenteral aminoglycosides or vancomycin induced this disorder.
Clinical manifestations range from mild to moderate diarrhea with lower abdominal cramping, to severe colitis (with or without pseudomembranes) accompanied by systemic manifestations (anorexia, malaise, fever) and toxic dilatation or perforation[3].

Drug induced rashes are the commonest side effect of many drugs. In general, the mechanisms are unknown, and only about 10% of such reactions result from true allergic mechanisms. Typical examples of drug induced rashes include fixed drug eruptions, erythematous maculopapular eruption due to penicillin: rashes of this kind are by far the most common reactions to drugs, and exfoliative dermatitis Erythema multiforme due to sulphonamide treatment[4].

Other Examples of ADRs Associated with Antibiotic Use

The Penicillin family of drugs is usually well tolerated, but they have been associated with a wide range of hypersensitivity reactions which include fever, rash (maculopapular and urticarial), anaphylaxis, exfoliative dermatitis, erythema multiforme, serum sickness, and hemolytic anemia[5].

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[1] Daniel Vervloet, Stephen Durham, ABC of allergies: Adverse reactions to drugs. BMJ 1998;316:1511-1514 (16 May)
[2] Richard A.Gleckman, John S Czachor, Antibiotic Side Effects,Seminars in Respiratory and critical care Medicine. http://www.medscape.com/view article/41087
[3] Richard A.Gleckman,MD; fernado Borrego , MD Adverse reactions to antibiotics:Clues to recognizing, understanding and avoiding them, Vol 101/No 4/April 1997/Postgraduate medicine Antimicrobial therapy symposium.
[4] Ibid 1
[5] Ibid 2

Sensitization to this class of drugs, usually results from previous exposure to one of the drugs or its degradation products, which are haptens and can form antigenic complexes with proteins and polypeptides[6]. When administered intravenously in high doses, particularly to patients with renal impairment, they have the potential to cause central nervous system toxicity, manifested by myoclonic jerks, seizures or coma. Specific members of the penicillin family have been identified with particular adverse reactions: ampicillin, amoxicillin, and amoxicillin/clavulanate with diarrhea and C. *difficile* colitis, as well as rash when prescribed to the patient with chronic lymphocytic leukemia[7].

The Cephalosporins have proven to be very safe compounds and this is one explanation for their wide appeal. Untoward events attributed to the cephalosporins have included diarrhea, pseudo-membranous colitis, and rarely, hypersensitivity reactions including drug fever, rash, interstitial nephritis or immediate life-threatening events. Specific members of the cephalosporin family of compounds have been identified with particular adverse reactions: ceftriaxone, with diarrhea; ceftriaxone with reversible biliary sludge[8].

The Tetracyclines: Doxycycline has been associated with diarrhea and, infrequently, photosensitivity; rash; hepatitis; and particularly in elderly patients, esophageal ulcerations or strictures[9].

Aminoglycosides: Concerns regarding administration of the aminoglycosides include nephrotoxicity, specifically nonoliguric acute renal failure, ototoxicity, both the auditory and vestibular components, and neuromuscular blockade, a rare event that has developed in patients with myasthenia gravis, renal disease, hypocalcemia, or hypermagnesemia.

Factors contributing to nephrotoxicity include duration of therapy, older age, liver disease, shock and the coadministration of drugs that have the potential to cause nephrotoxicity, such as amphotericin B, cisplatinum, cyclosporine, and ethacrynic acid. Limited data indicate that tobramycin is less nephrotoxic than gentamicin and that nephrotoxicity is reduced by a once per day dosing regimen. Factors contributing to ototoxicity include hypovolemia, total dose administered, renal impairment, liver dysfunction, elevated serum trough concentrations, cisplatinum, furosemide, and ethacrynic acid[10].

Sulphonamides: The antimicrobial activity of the combination of **Trimethoprim and Sulfamethoxazole** results from its actions on two steps of the enzymatic pathway for the synthesis of tetrahydrofolic acid, a folic acid precursor which is required by both mammalian and bacterial cells. A case of selective toxicity for micro organisms is thus achieved because of the ability of the mammalian cells to use preformed folate from the diet. Therefore, only in rare cases could this combination induce folate deficiency in normal persons[11].

The most common side effects precipitated by **Trimethoprim and Sulfamethoxazole** are rash, fever and gastrointestinal adverse reactions. Additional rare untoward events include nephrotoxicity, hyperkalemia, hematologic derangements (neutropenia, thrombocytopenia, agranulocytosis, aplastic anemia, and megaloblastic anemia), hepatitis, pancreatitis, pseudomembranous colitis, and adverse CNS events (headache, insomnia, vertigo, ataxia, and aseptic meningitis).

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[6] American Society of Health System Pharmacists, AHSP Drug Information 2005 edition, page 273
[7] Ibid 2
[8] Ibid 2
[9] Ibid 2
[10] Ibid 2
[11] The Pharmacological Basis of therapeutics,Goodman & Giman's Tenth Edition, page 1176-1179

Macrolides : Adverse events attributed to the macrolides have includes nausea, vomiting, abdominal pain, diarrhea, and, rarely, antibiotic-associated colitis, pancreatitis, cholestatic jaundice, acute hepatitis, abnormal taste (clarithromycin), and reversible ototoxicity. Clarithromycin and azithromycin cause fewer gastrointestinal adverse events than does erythromycin[12].

Fluoroquinolones: The most common adverse events attributed to the fluoroquinolones are gastrointestinal symptoms, nervous system complaints (headache, dizziness, insomnia, agitation, and hallucinations), and allergic reactions (rash and pruritus). Rare adverse effects include seizures, elevations of liver enzymes, and tendinopathy[13].

WITHDRAWAL OF LAPDAP AND THE STOPPAGE OF THE PHASE III CLINICAL TRIAL INVOLVING CHLORPROGUANIL, DAPSONE AND ARTESUNATE IN NIGERIA

The inexorable spread of resistance to affordable antimalarial drugs poses one of the largest public health problems for Africa. Many countries are faced with the challenge of when to change from chloroquine as first-line treatment or what to do about resistance to sulphadoxine-pyrimethamine (SP). New treatments for non-severe falciparum malaria are desperately needed in Africa to replace SP, one of the last affordable drugs.

Lapdap™ is a GlaxoSmithKline (GSK) antimalarial product which is a combination of Chlorproguanil and Dapsone (CD). LapDap™ is active against African SP-resistant falciparum strains and has a much shorter plasma half-life than SP, hence a low propensity to select resistant parasites. It is seen as an alternative or replacement for sulphadoxine-pyrimethamine (SP).

CD (LapDap™) was granted marketing authorization in July 2003 by the United Kingdom Medicines and Healthcare Products Regulatory Agency for the treatment of uncomplicated falciparum malaria.
CD (LapDap™) is however, contraindicated in patients with known glucose-6-phosphate dehydrogenase (G6PD) deficiency.

In view of the potential widespread use of CD (LapDap™) in malaria endemic sub-Saharan Africa, the high prevalence of G6PD deficiency in the region (estimated to affect around 10-25% of the population in sub-Saharan Africa) and the limited availability of screening tests for this genetic condition in Africa, WHO had undertaken a safety assessment of the product in 2004, to provide recommendations on the safe use of CD (LapDap™) in Africa.

The WHO expert group cautioned against the use of the medicine in G6PD deficient patients and made the following recommendations:

1. This medicine should be used only if a diagnosis of malaria is confirmed.

2. CD should be used only after severe anaemia (haemoglobin concentration < 5 g/dl) and G6PD deficiency have been excluded by appropriate tests. In patients with a haemoglobin concentration of 7 g/dl, administration of CD should be considered with caution and should be undertaken only under

[12] Ibid 2
[13] Ibid 2

clinical supervision, with monitoring of the haemoglobin concentration. The diagnosis of methaemoglobinaemia is less important.

3. In areas where G6PD deficiency is prevalent but appropriate tests are not available, an alternative antimalarial medicine should be used.

4. If there is no suitable alternative, CD should be used but in cognizance of the haematological risks associated with this medicine.

The group also advised that these recommendations should be reconsidered when more data become available from pharmacovigilance and active post-marketing surveillance.
The WHO safety assessment report also provided a series of recommendations for ongoing and planned clinical trials as well as phase IV studies to gather the necessary evidence on safety of CD (LapDap™), including in malaria patients with G6PD deficiency.
However, several CD (LapDap™) phase IV studies which started in African countries did not continue beyond April 2006 due to low utilization of this medicine. Research on the safety aspects mainly continued as part of the Medicines for Malaria Venture (MMV)- sponsored studies on chlorproguanil-dapsone-artesunate (CDA).

In Nigeria, two strengths of the products were registered on the 31st July 2003 with NAFDAC registration numbers 04-4064(Lapdap 15mg/18.75mg) and 04-4062(Lapdap 80mg/100mg) respectively. The license will expire in July 2008.

Nevertheless, Post Marketing Surveillance (PMS) reports on CD (LapDap™) submitted by GSK between 2005 and 2006 revealed Serious Adverse Events (SAEs) associated with the use of Lapdap. The company was therefore notified in a letter to submit Update Safety Reports on Lapdap in view of the Serious Adverse Events observed.
GSK was also advised to voluntarily suspend further importation and marketing of Lapdap in view of the evolving safety concerns on the use of Lapdap to which they complied.
Based on the new malarial policy on the use of ACTs, their proposed phase IV trial for Lapdap in Nigeria to address concerns on safety was suspended hence the development of Lapdap-Artesunate (CDA) by GSK.

Though NAFDAC was aware of the possibility of haemolysis following the use of Lapdap particularly in populations that are G6PD deficient, very limited scientific data to prove the causal relationship between Lapdap and haemolysis in type A- G6PD deficiency (The African subtype) was available. There was need to ascertain the level of exposure hence approval was given to GSK to conduct the proposed phase III Clinical trial in order to address these uncertainties.

GSK planned to design the protocol of the CDA trial to ensure that Adverse Drug Reactions were detected at this stage and not during Post Marketing Surveillance (PMS) as occurred in the case of Lapdap. The design was to provide for:

- Genome sequencing test to identify specific variant of G6PD deficiency in participants which would reveal the risk and the extent of risk to haemolysis associated with established variants.
- Home visits to check on subjects at home in order to ensure that there were no life-threatening drug reactions and to ensure continuity of the trial.

- Establishment of a Data Safety Monitoring Committee (DSMC) whose responsibility was to monitor safety issues with respect to the trial and take appropriate remedial action to protect the participants.

Chlorproguanil-dapsone-artesunate(Dacart™)

GSK's multi-center, double-blind Phase III clinical trial of chlorproguanil-dapsone-artesunate (CDA) versus the combination antimalarial lumefantrine-artemether (Coartem®) in Africa suggest a strong association between haemolytic anaemia and CDA treatment for uncomplicated falciparum malaria in G6PD deficient patients.

The study included 1372 patients. Study results showed a significant reduction in haemoglobin due to haemolytic anaemia in patients with G6PD deficiency, with lowest levels of haemoglobin occurring seven days after treatment.

At day 7, 35% of the patients with G6PD deficiency treated with CDA had a reduction in haemoglobin of more than 2 g/dl compared to 8% of patients treated with Coartem®, and 10% of the patients with G6PD deficiency treated with CDA had a reduction of more than 4 g/dl compared to 0% of patients treated with Coartem®. 38% of the male patients with G6PD deficiency had severe anaemia after treatment with CDA, compared to 0% in the group treated with Coartem®. In total, 15 patients had severe post-treatment haemolysis requiring blood transfusion in the study: all 15 were in the CDA treated group, 13 of whom were G6PD deficient.

GSK has commenced a product recall process at pharmacy level in Kenya, for LapDap™ and has voluntarily terminated the phase III clinical trial for CDA going on in Nigeria. These decisions were based on data from two Phase III clinical trials assessing the efficacy and safety of CDA (Dacart™) and CD (LapDap™); significant reductions of haemoglobin levels in patients with G6PD deficiency have been observed with both CDA and CD.

References:

Press Release. GlaxoSmithKline and Medicines for Malaria Venture, 29 February 2008, London, UK; Geneva, Switzerland.

Review of the safety of chlorproguanil-dapsone in the treatment of uncomplicated falciparum malaria in Africa: Report of a Technical Consultation convened by the World Health Organization. WHO, 2005, Switzerland (http://www.who.int/malaria/docs/LapDap.pdf).

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