



PHARMACOVIGILANCE - POST MARKETING SURVEILLANCE NEWS

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Editor's Note

I wish to thank all our numerous stakeholders who have been working tirelessly with the National Pharmacovigilance Centre (NPC) to ensure the safe use of medicines in Nigeria. The NPC is committed to sending quarterly newsletter to its stakeholders. The objectives of the Newsletter are to disseminate information on pharmacovigilance activities nationally and globally, to educate stakeholders on medicine safety issues, to promote rational use of drugs and to promote spontaneous reporting. This third quarter Newsletter focuses on ***Pharmacovigilance of Antidiabetic Drugs***. We encourage all Health Care Professionals, Marketing Authorization Holders and other stakeholders to continue to report all adverse drug reactions. Your valued comments and acknowledgement of receipt of this issue through our email addresses (nafdac_npc@yahoo.com; pharmacovigilance@nafdac.gov.ng) would be most appreciated.

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Text any DRUG RELATED PROBLEM to SHORT CODE 20543 (for free on MTN, GLO and Etisalat) for action by the Pharmacovigilance Centre

PHARMACOVIGILANCE OF ANTIDIABETIC DRUGS

Diabetes is one of the major causes of illnesses and deaths globally, and it affects many regardless of age or race. This disease can contribute to other health complications such as heart disease, kidney disease and blindness if not properly treated. Diabetes Mellitus, often referred to as diabetes, describes a group of metabolic diseases in which the person has high blood glucose (blood sugar), either because insulin production is inadequate, or because the body's cells do not respond properly to insulin, or both⁽¹⁾. Patients with high blood sugar will typically experience polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger).

Over the years, antidiabetic drugs have been developed to stabilise/control blood glucose levels and generally manage the disease. Although prescription drugs are subject to extensive, premarket safety testing prior to approval, adverse drug reactions (ADRs) not identified in preclinical and clinical testing may become apparent following their introduction into the market and their subsequent use within the highly heterogeneous general population. Appropriate and effective management of ADR (i.e. Pharmacovigilance) is the best way to safeguard public health⁽²⁾.

Anti-diabetic drugs classification and potential side effects

Like all medications, there may be side effects in the use of anti-diabetic drugs. A side effect can be defined as any unintended effect of a pharmaceutical product occurring at doses normally used in humans, which is related to the pharmacological properties of the drug. Side effects are related to the known properties of the drug and can often be predicted⁽³⁾. For example, below are some of the antidiabetic drugs and their possible side effects:

Sulfonylureas: low blood sugar (hypoglycaemia), stomach upset, skin rash/ itching, weight gain.

Biguanides / Metformin: sickness with alcohol, kidney complications, stomach upset, tiredness or dizziness, metallic taste.

Alpha – glucosidase inhibitors: gas, bloating and diarrhoea.

Thiazolidinediones: weight gain, risk of liver disease, anaemia risk, risk of oedema and heart failure.

Rosiglitazone, a thiazolidinedione has been withdrawn from several markets due to its cardiovascular risk factors; this risk may also be associated with pioglitazone, another drug in this class.⁽⁴⁾

Meglitinides: weight gain, low blood sugar.

A review of some Operational Studies with Antidiabetic Drugs

The use of antidiabetic drugs has been on the increase and reports of serious adverse effects associated with their use have become a source of concern. However, in Nigeria, there is paucity of information on outcomes of therapy and adverse drug reaction (ADR) reporting among diabetic patients.

A study on drug therapy problems (DTPs) in patients with Type 2 diabetes mellitus (T2DM) was carried out at Nnamdi Azikiwe University Teaching Hospital (NAUTH) Nnewi, Anambra State, South Eastern Nigeria between February and September 2013. Analysis conducted on randomly selected records of 399 T2DM patients comprised males 208 (52.1%), females 188(47.9%). Age range from 35 to 91 years and usage of Metformin (27.6%) & glibenclamide (22.5%). A combination of metformin and glibenclamide was used in 6.6% of the patients and insulin was prescribed for 17.1%. Hypoglycaemia was recorded as the most common ADR recorded in 49 patients, 12.3% of the survey group⁽⁵⁾.

Another study carried out in Sicily, Italy on type 2 diabetes mellitus (T2DM) patients who started any antidiabetic drug in the period of October 1st, 2010 – December 31st, 2012, with reports from the Sicilian Pharmacovigilance Centre database. The study compared ADRs reported to the co-ordinating centre via questionnaire. Results showed that out of 1687 T2DM patients under study, 186 (11%) patients experienced at least one ADR. The most frequently involved antidiabetic drugs were biguanides (29.6%), combinations of oral hypoglycaemic drugs (17.6%) and incretins (16.6%). The Main ADRs were hypoglycaemia, especially with insulin and gastrointestinal events (nausea/ vomiting, diarrhoea, and abdominal pain) for biguanides and metiglinides ⁽⁶⁾.

A retrospective investigation by Raschi E *et. al.* into the publicly available FDA Adverse Event Reporting System (FDA_AERS) database between 2004-2009 periods revealed cases of possible association between antidiabetic medications and pancreatitis. Reports of pancreatitis were defined as cases while antidiabetic associated reports were considered non-cases. Reports retrieved showed 86,938 related to antidiabetics, corresponding to 159,226 drug-report combinations of exenatide and sitagliptin: 2,625 cases and 156,601 non-cases. Significant disproportionalities in reporting were observed with exanatide, temporal analysis found that relevant FDA warnings greatly influenced reporting of pancreatitis. It was therefore recommended to avoid transforming a pharmacovigilance signal of alert automatically to public alarm. ⁽⁷⁾

Conclusion

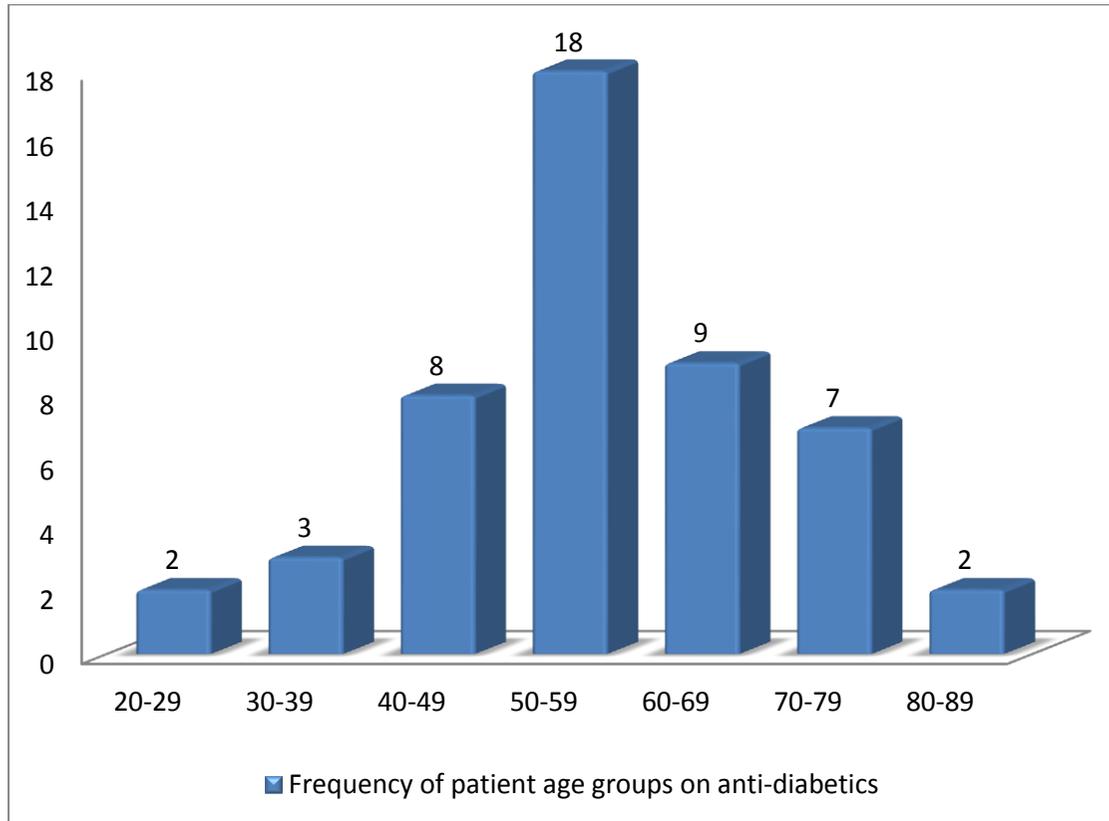
The research findings cited above has shown clearly that ADRs of these antidiabetic drugs cannot be completely avoided but adequately managed through prompt identification and reporting. Lack of adherence to diabetic therapy contributes

to inadequate glycemic control; this often results from self-medication and overdosing, and complicates ADR monitoring. There is therefore need for effective counselling and diabetic education of patients to enhance their awareness and knowledge of the condition for improved adherence. Appropriate medication, alongside a healthy diet and exercise routine will help people living with diabetes to maintain stable blood glucose levels. Depending on reactions to prescribed drugs, physicians should be promptly informed for advice or changes where necessary and the ADRs reported to NAFDAC.

ADVERSE DRUG REACTIONS ASSOCIATED WITH HYPOGLYCEAMIC DRUGS AND INSULIN (REPORT FROM THE NPC DATABASE)

Reports of spontaneous adverse reactions (individual case safety report – ICSRs), received by the National Pharmacovigilance Centre (NPC) from 2004 to August 2014 were retrospectively studied and analysed. A total of 49 patients (63% female and 37% male) placed on oral hypoglycaemic drugs and patients with type 1 diabetes, placed on insulin that developed adverse drug events were reported to the National Pharmacovigilance Centre (NPC). Majority of the patients, 83.7% were placed on oral hypoglycaemic drugs while only 16.3% of the patients were placed on insulin (table 1.1). Age group of the reported cases ranged from 20years to 89 years and majority of the events occurred within the age group of 50 to 59 years (fig 1.1).

Fig 1.1 Frequency of patient age groups on anti-diabetic drugs



Source: Data generated from the NPC database

Seven patients were placed on insulin mono-therapy while two of the patients were concomitantly placed on antibiotics and one on antihypertensive (table 1.2). Adverse event reported for patients placed on insulin include polyphagia weakness, profuse sweating(hyperhidrosis), tachycardia, dizziness, restlessness, irrational behaviour, red eye and itching (table 1.1).

Table 1.1 Insulin regimens and associated ADRs as reported

Suspected Medicines	Concomitant Medicines	Adverse Drug Reactions
Insulin mono-therapy (7)	None	Polyphagia, weakness, sweating profusely, tachycardia, dizziness, restlessness, irrational behaviour, red eye, itching, headache, hyperhidrosis
Insulin (3)	a) Augmentin, levofloxacin b) Lisinopril, nifedipine c) Ceftriaxone, metronidazole	Itching, headache, spots on face Red eye, weakness Profuse sweating

Source: Data generated from the NPC database

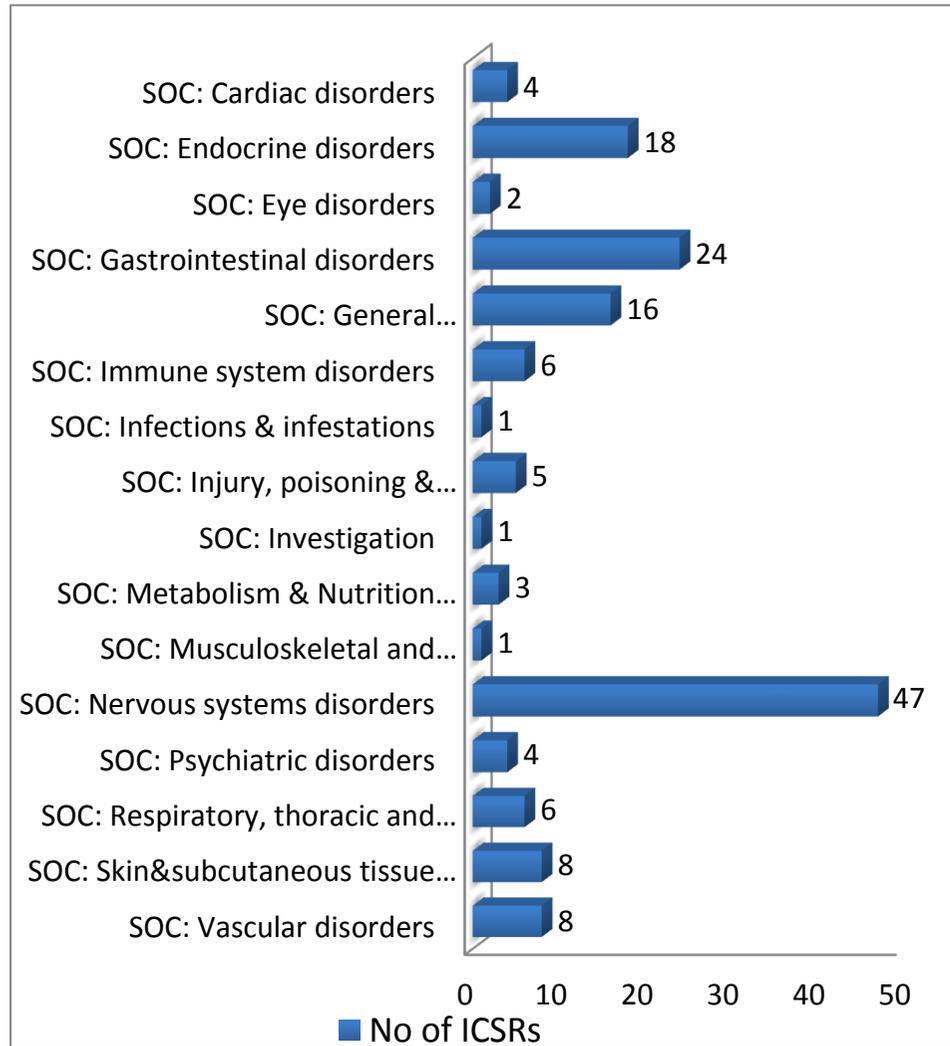
The suspected mono-therapy oral hypoglycaemic drugs reported include metformin (18), glibenclamide (9) and glimepiride (1). However, four individual case safety reports (ICSR) indicated metformin and glibenclamide (MG) as suspected drugs and two indicated MG and other antihypertensive drugs as suspected drugs (table 1.1). Adverse event reported for patients on metformin includes headache, rashes, restlessness, irrational behaviour, epigastric pain, palpitation, weakness, headache, dizziness, heartburn, cough, insomnia, malaise, diarrhoea, dizziness, migraine and itching (table 1.1- detailed description of adverse events reported on metformin and drugs that were concomitantly prescribed).

Table 1.2 Oral hypoglycaemic regimen and associated ADR

Suspected medicines	Concomitant medicine	Adverse drug reactions
Metformin (22)	Vasoprin (11), lisinopril (3), nifedipine (2), amlodipine (2), glibenclamide (7), moduretic (2), amiloride, losartan (2), bendroflumethiazide, hydrochlorothiazide, carbamazepine, digoxin, furosemide, glimepiride, imipramine, cholestyramine multivitamin, fluvastatin, bendroflumethiazide,	Headache, rashes, restlessness, dyspepsia, epigastric pain, palpitation, weakness, dizziness, migraine, vomiting, diarrhoea, migraine, visual disturbance, breathlessness, irrational behaviour, numbness, cough, nausea, insomnia, nausea, malaise, diarrhoea, heartburn, ptyalism, fainting, abdominal pain, hyperthermia, diaphoresis
Glibenclamide(10)	Metformin (4), amlodipine, lisinopril, nifedipine (2), paracetamol (2), pregabalin	Coma (4), Hypoglycaemia (4), palpitation, dizziness, numbness
Glimepiride (1)	None	Headache, dizziness, palpitation, hot flushes
Metformin &Glibenclamide (4)	Furosemide, aspirin, digitoxin	Dizziness, diaphoresis, hypoglycaemia, tremor
Metformin, lisinopril, atenolol, bromazepam(1)	Aspirin	Erythematous rash
Metformin, lisinopril, glibenclamide, acetylsalicylic acid	Chloroquine, metamizole	Headache, palpitation, restlessness, vomiting, diaphoresis

Source: Data generated from the NPC database

SYSTEM ORGAN CLASSIFICATION OF REPORTED ADR ASSOCIATED WITH ANTIDIABETIC MEDICATION



Source: Data generated from the NPC database

It is worth noting that almost all the patients on glibenclamide were either comatose or experienced hypoglycaemia, with the reactions affecting either the endocrine or the nervous system (system organ class of the reported adverse events on patients placed on glibenclamide: endocrine and nervous system). This has been attributed to the pharmacokinetic properties of glibenclamide because its hypoglycemic effects last for 24 hours. In addition, glibenclamide is associated predominantly with the insulin secretagogues. Adverse Drug Reactions to antidiabetic drugs could be viewed as an important cause of long-term morbidity, and influence adherence to prescribed medicines sometimes necessitating the use of ancillary medication or the suspension of treatment.

ADVERSE DRUG REACTIONS FROM REACTIONS WEEKLY

METFORMIN

Lactic Acidosis: 16 cases reports

Four men and 12 Women aged 58-88 years developed lactic acidosis during treatment with metformin for type 2 diabetes mellitus.

All patients had been receiving metformin 850-2550 mg/day [routes not stated] for an unspecified duration when they developed lactic acidosis. Risk factors were present in 12 patients; these include chronic renal failure (8 patients), heart failure (4), chronic obstruction pulmonary disease (3) and alcohol abuse (1). Their admission diagnoses include shock, liver failure, acute renal failure, myocardial infarction, bradycardia, dehydration and pneumonia. Lactate and arterial pH levels were 5.8-23.2 mmol/l and 6.77- 7.33, respectively. On admission, creatinine levels ranged from 86 to 1039 μ mol/L and the

modification of diet in renal disease(MDRD) estimated glomerular filtration rate from 3 to 56 ml/min/1.73m² . Serum metformin concentrations range from 0.4 to 44.0mg/L.

Treatment included haemodialysis, continuous venovenous haemofiltration and continuous venovenous haemodiafiltration. Eleven out of the 16 patients survived, and five died.

Van Berlo-Van De Laar IRF, et. al. Metformin associated lactic acidosis: incidence and clinical correlation with metformin serum concentration measurements. Journal of clinical clinical pharmacy and therapeutics 36:376-382, No. 3, Jun2011. Available from:<http://dx.doi.org/10.1111/j.1365-2710.2010.01192.x>- Netherlands

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Metformin/ tenofovir

Acute renal failure lactic acidosis in an elderly patient: Case report

A 74 year old man with type 2 diabetes mellitus and HIV infection developed acute renal failure and lactic acidosis during treatment with metformin and tenofovir (routes and durations of treatment to reaction onset not stated).

The man was hospitalised with tachypnoea, abdominal zoster – like pain, anuria, nausea and vomiting. His current medications included metformin 850mg three times daily, as well as HARRT with efavirenz, emtricitabine and tenofovir 300mg daily, which had been recently started. On examination, signs of dehydration were observed and his abdomen was tender on palpation. Arterial blood gas analysis revealed metabolic acidosis with a lactate level of 13.5 mmol/L and he required oxygen due to low oxygen saturation. Laboratory findings included elevated levels of urea, creatinine, and potassium. A chest x-ray demonstrated hilar enlargement.

Sodium chloride and bicarbonate were initiated, as well as empirical antimicrobial therapy and furosemide . Despite treatment, the man remained oliguric. He subsequently underwent nine sessions of haemofiltration. His lactic acidosis resolved within a few days, and his urine output progressively improved. Laboratory parameters had normalised after 40 days.

Author's comment: "We conclude that renal function should be carefully monitored in patients on metformin especially when concomitant potentially nephrotoxic therapy is administered".

Aperis G, et al. Lactic acidosis after concomitant treatment with metformin and tenofovir in a patient with HIV infection. Journal of Renal care 37: 25-9, No. 1, Mar 2011. Available from: URL: <http://dx.doi.org/10.1111/j.1755-6686.2011.00209.x>

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