National Drug Authrotiy

Pharmacovigilance

ISSUE 4

Bulletin

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EDITORIAL

Dear readers,

Pharmacovigilance, based on the principle of "do no harm", involves continuous surveillance of medicines beyond the scope of unexpected adverse drug reactions. As in the Gentamycin related cases presented in this bulletin, ADR reporting can contribute to the optimization of therapy and risk minimization by easily and quickly identifying and reporting suspicions that can be investigated further

A number of safety signals have been presented, as well as the summary of adverse drug reaction reports received at NDA the period July to September 2018

I would like to take this opportunity to thank all the health workers who have diligently reported adverse drug reactions to NDA and who consider pharmacovigilance as a key component in clinical care.

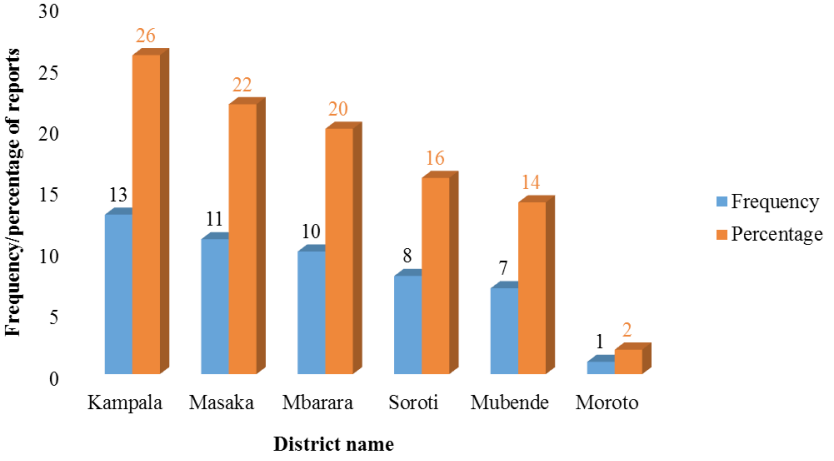
Manager, Pharmacovigilance

National Drug authority

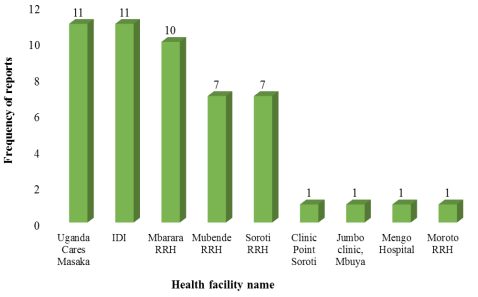
Victoria Nambasa

ADVERSE DRUG REACTION STATISTICS

NDA received a total of 50 ADR reports in the period of July – September 2018 from various districts and health facilities and all the case were reported to be serious. Kampala district reported highest (26%. n=13) followed by Masaka district (22%;n=11), as shown in figure 1 below.



During this period, most reports were received from Uganda cares Masaka (n=11) and IDI (n=11) followed by Mbarara Regional Referral Hospital (n=10) as shown in the figure 2 to the right.



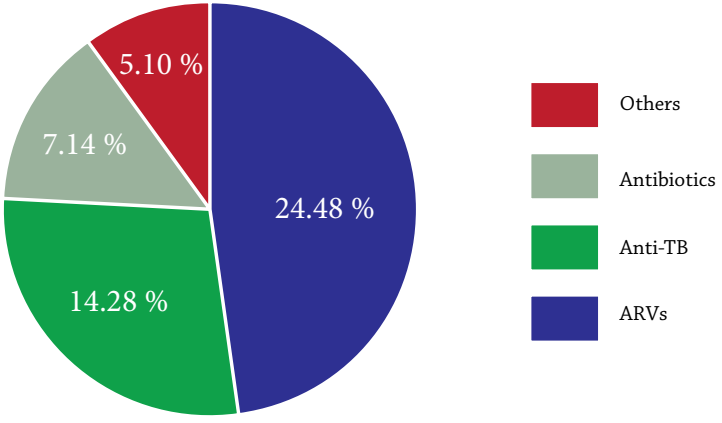
Over all, Pharmacists submitted most reports (n=20, 40%) followed by clinical medical officer (n=14, 28%), Medical officer (n=11, 22%), nurse (n=3, 6%), and others (n=2, 4%).

The most preferred mode of reporting was the physical ADR form (n=36, 72%) whereas 10 reports (20%) were reported online and 4 reports via vigiflow (8%

Characteristics of ADR reports

All the reports were considered serious due to their life threatening nature of presentation. Overall ARVs were reported most (48%;n=24),followed by Anti-TBs(28%;n=14) as shown in figure 3.

Figure 3: Reporting rates per therapeutic category



Antibiotics mainly caused skin reactions (n=4), Anti-TB drugs were mostly associated with Ototoxicity/Hearing loss (n=8), Hepatotoxicity (n=2) and Hypothyroidism (n=2), whereas ARVs were associated with renal toxicity/Increased creatinine (n=6), rash (n=4), hepatotoxicity (n=3) and hyperemesis (n=2). Table 1 summarises the Drug –reaction combination frequencies.

Table 1. Drug-Reaction Pairs

DRUG	REACTION	FREQUENCY OF REPORTS
Amoxicillin	Rash	1
Antiserum	Hypersensitivity (Dyspnea, Profuse sweating, shivering, Lethargy)	1
AZT/3TC/EFV	Psychotic episodes	1
AZT/TDF/NVP	Skin Hyperpigmentation	1
Bahati herbal mouth wash	Fever	1
Benzylpenicillin	Oral lesions	1
Ceftriaxone/Ampicillin injection, Ceftriaxone/Sulbactam	Rash	3
CTX/TDF/3TC	Elevated alkaline phosphatase, arthralgia,	1
	Renal toxicity/Increased creatinine	1
CTX/TDF/3TC/EFV	Rash	1
Efavirenz	Hepatotoxicity	2
Enoxaparin(heparin)	Profuse bleeding	1
Ethionamide	Hypothroidism	2
Gentamicin	Headache, dizziness, nausea, restlessness	1
Isoniazid	Hepatotoxicity	1
Kanamycin	Ototoxicity/Hearing loss	8
Levofloxacin	Achilles tendinitis	1
Misoprostol	Fever	1
Pyrazinamide	Hepatotoxicity	1
Raltegravir	Rash	1
RHZE	Deep Jaundice and Vomiting	1
	Rash	1
Snake Venom antiserum (poly-valent)	Anaphylaxis	1
TDF/3TC	Decreased Glomerula Filtration Rate	1
	hypotension	1

Table 2. Drug-Reaction Pairs condtinued

DRUG	REACTION	FREQUENCY OF REPORTS
TDF/3TC/EFV	Headache, dizziness, nausea, restlessness	1
	Peri-orbital swelling/Dizziness	1
	Rash	2
Tenofovir	Hyperemesis	1
	Osteoporosis	1
	Reduced bone density	1
	Renal toxicity/Increased creatinine	5
Zidovudine	Hepatotoxicity	2
	Hyperemesis	1

SAFETY UPDATES: GENTAMYCIN INJECTION

Increased reports of unlabelled serious drug reactions associated with gentamycin were received at the NPC.

Gentamycin Sulphate injection in Uganda is indicated in management of serious bacterial infections in both adults and children. Between May and October 2018, the NPC received 15 reports regarding adverse events associated with multiple Gentamycin injection brands and batches from various health facilities. 14 of the patients experienced acute severe throbbing headache accompanied with blurred vision, vomiting and palpitations. One case in addition had loss of consciousness whereas one patient was reported to have had raised blood pressure.

The reports were life threatening, occurring immediately after administration of the drug at recommended doses. No potential drug interactions were cited.

Investigations

This reported severe headache is not a well characterised reaction as per the review of the summary of product characteristics. The British National Formularly lists headache as a very rare reaction (1:10,000). The WHO global database indicated 221 cases of headache associated with gentamicin, with 15 cases from Africa excluding the Ugandan cases.

Regulatory actions;

As NDA continues to investigate the occurence of these ADRs, some regulatory actions have been undertaken including

1. Issuing of "**Dear Healthcare Provider**" reminding health workers to monitor patients being administered Gentamycin and subsequently reporting any abnoxious events.

2. The finished pharmaceutical products manufacturing sites were found to be cGMP non-compliant and subsequently all parenteral products from the three affected facilities were **recalled** from the market.

3. NDA advises all healthcare providers to use the product only when appropriate and monitoring for possible adverse events in patients is warranted.

SAFETY UPDATES: DOXYCYCLINE

Doxycycline is a tetracycline antibiotic used to treat a wide variety of bacterial infections, such as urinary tract infections, intestinal infections, eye infections among others as well as some protozoal infections.

Doxycycline has been notably reported and documented to cause various gastrointestinal adverse effects with esophagitis and esophageal ulcerations recorded among the most severe and yet commonest gastrointestinal adverse events.

These usually occur when the medication is taken shortly before bedtime and with little or no water. In the process of lying down, the pill can reflux back up into the esophagus, where it can irritate or even ulcerate the lining of the esophagus. Unfortunately, many health care professionals in Uganda are currently not familiar with this particular drug reaction.

The incidence of esophageal ulcers is greater for doxycycline capsules than with tablets. Studies have shown that doxycycline capsules remain three times longer in the esophagus than doxycycline tablets. The mechanism of esophageal mucosal injury induced by doxycycline capsules may be explained by their acidic effect, gelatinous sticky nature, increased mucosal concentration and intracellular toxicity.

The identification of symptoms such as odynophagia, retrosternal pain and dysphagia can be useful in the diagnosis of a doxycycline-induced esophageal ulceration.

Advice to health workers:

1. Advise patients to take doxycycline with a meal or with a large glass of water or other fluid.

2. Advise patients to remain in an upright position, for at least half an hour after drug administration and to avoid taking their medication immediately before going to bed. Take the medicine 1 hour before bedtime.

3. Counsel patients to report back any signs of esophageal discomfort.

4. Treat patients on doxycycline medication who show signs of esophageal ulceration with a proton-pump inhibitor (PPI) and/or a prokinetic agent.

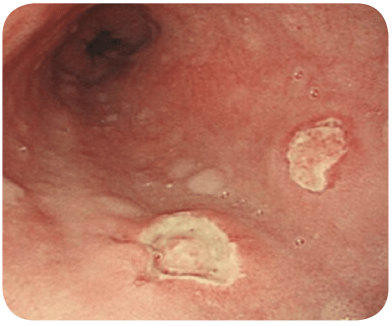


Image showing ulceration of the oesophagus

References.

Berger RS. A double-blind, multiple-dose, placebo-controlled, cross-over study to compare the incidence of gastrointestinal complaints in healthy subjects given Doryx R and Vibramycin R. J Clin Pharmacol. 1988; 28:367–370.

Bott S, Prakash C, McCallum RW. Medication-induced esophageal injury. Survey of the literature. Am J Gastroenterol 1987; 82: 758-763

Boyce HW. Drug-induced esophageal damage: diseases of medical progress. Gastrointest Endoscopy 1998; 47: 547-550

Marian Macsai, Gioconda Mojica, in Ocular Surface Disease: Cornea, Conjunctiva and Tear Film, 2013. Medical Management of Ocular Surface Disease.

Sloan B, Scheinfeld N. The use and safety of doxycycline hyclate and other second-generation tetracyclines. Expert Opin Drug Saf. 2008; 7:571–577. [PubMed]

SIGNALS FOR CONTINUED VIGILANCE.

Artemether/Lumefantrine linked with Stevens-Johnshon syndrome:

Background

Fixed-dose combinations of Artemether/Lumefantrine (AL) are available in Uganda as the first line treatments of uncomplicated malaria.

A signal has been identified of Stevens-Johnson syndrome (SJS) potentially associated with Artemether/Lumefantrine (AL). Cutaneous reaction terms describing conditions with a clinical closeness to SJS are included in labeling for AL. The US labeling for AL mentions serious skin reactions (bullous eruption) in the post marketing experience.

Based on the WHO global database, there are several reports on this drug-ADR combination however the available information is not enough to exclude other explanations.

No reports of SJS have yet been received at NDA probably due to low reporting practices among healthcare workers.

Conclusion

While a firm conclusion on causality may not be drawn, NDA would like to advise health care providers to be aware of the possibility of SJS occurring in patients taking AL ,Patients should be monitored and encouraged to reporting any occurrence cutaneous reactions.

Reference

Uppsala Monitoring Center. Signal November 2017

Lamivudine and decreased Hearing

Background

Lamivudine is part of the first line, highly active antiretroviral therapy (HAART) regimen in Uganda, and also for the treatment of hepatitis B. A report from The WHO centre for drug monitoring indicated a signal of lamivudine with a possible causal relationship with decreased hearing. This adverse reaction is not listed among the known reactions associated with lamivudine.

Despite the inability to fully dissociate the effects like other co-administered ARVs, ageing, infection, and naturally occurring hearing loss, the evidence is suggestive of a possible causal effect relationship between lamivudine and hearing combination.

Conclusion

While the underlying primary disease in HIV/AIDS patients and other factors remains a possible cause, Lamivudine should be given due consideration especially in susceptible patients. NDA advises monitoring and reporting suspected hearing loss in patients taking Lamuvidine based regimens.

References

Uppsala Monitoring Center. Signal Octomber 2016

DID YOU KNOW

MEDICINE POISONING ANTI DOTES

An antidote is a drug, chelating substance, or a chemical that counteracts /neutralizes the effects of another drug or a poison.

There are dozens of different antidotes; however, some may only counteract one particular drug, whereas others (such as charcoal) may help reduce the toxicity of numerous drugs.

Most antidotes are not 100% effective, and fatalities may still occur even when an antidote has been given.

Don't assume that over-the-counter medications are safe even if taken in excess.

Consult a health care worker if you or your child takes many pills by accident or intentionally without waiting for symptoms to develop.

When taking the person to the hospital' take all the suspected medicine bottles, containers etc with you.

Common Antidotes

- **Acetylcysteine** for acetaminophen poisoning
- **Activated charcoal** for most poisons
- **Atropine** for organophosphates and carbamates poisoning like insecticide poisoning.
- **Digoxin immune fab** for digoxin toxicity
- **Dimercaprol** for arsenic, gold, or inorganic mercury poisoning.
- **Flumazenil** for benzodiazepine overdose
- **Methylene blue** for drug-induced methemoglobinemia.
- **Naloxone** for opioid overdose.
- **Pralidoxime** for poisoning by anti-cholinesterase nerve agents
- **Vitamin K** for Warfarin

COMMON DRUG INTERACTIONS

A drug interaction is a reaction between two (or more) drugs or between a drug and a food or beverage. A drug interaction can decrease or increase the action of a drug or cause unwanted side effects.

Explain to the patient if there are any medications/food/ beverages to avoid when you are starting them on any new medication.

DRUG INTERACTIONS

- **Sildenafil** and Isosorbide Mononitrare. Sildenafil may markedly increase the hypotensive effects of Isosorbide monohydrate
- Theophylline and **Ciprofloxacin**. The toxicity of Theophylline is increased
- Methotrexate and **Probenecid**. leads to 2 to 3-fold increase in Methotrexate levels
- **Bromocriptine** and Pseudoephedrine can lead to severe peripheral vasoconstriction, ventricular tachycardia, seizures and possibly death.
- **Metronidazole** oral and Warfarin. Oral metronidazole increases the levels of warfarin by slowing its metabolism
- Carbamazepine and **Fluconazole** leads to increased carbamazepine levels
- Amiodarone and **Haloperidole** can cause arrhythmias
- Simvastatin and **Ketoconazole** increases statin toxicity.

If you have any comments or feedback on any of the articles in this bulletin, we would be pleased to receive them at druginfo@nda.or.ug/ dps@nda.or.ug

To report Adverse Drug Reactions complete the Adverse Drug Reaction form and return it to any NDA office near you or send a direct online report at

https://primaryreporting.who-umc.org/Reporting/Reporter?OrganizationID=UG, Fax: +256-414-655.60.80 E-mail: druginfo@nda.or.ug or whatsapp on 0791415555

You can visit us at: www.nda.or.ug