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Editorial

Happy New Year!

A big thank you toall health workers and patients who have shared information with us through reporting drug related events. It is our sincere hope that in this bulletin we have shown that we are making progress, meeting new challenges and helping the patients more than ever before. Our appreciation also goes to those who have contributed to this bulletin. Once again, a glimpse at the new safety information of some of the commonly used medicines is discussed.

Helen Byomire – Ndagije

From Data to Decisions: Building a Global Safety Culture: The Importance of Pharmacovigilance

The Thalidomide disaster in his history is one of the catastrophes that influenced the development of medicine regulation. This disaster led to establishment of safety committees and voluntary adverse drug reaction reporting systems .Up to today, the need for pharmacovigilance

systems are considered important and health workers and consumers are encouraged to report adverse events to regulatory agencies. However, one would ask why report when medicines are thoroughly checked for safety and efficacy before being authorized for use on the market.

Drug safety knowledge is accrued throughout the lifecycle of a drug and this process is iterative (one finding leads to another), incremental (one step at a time) and essential (needed for the safe use of the drug).

THE DEVELOPMENT STAGE

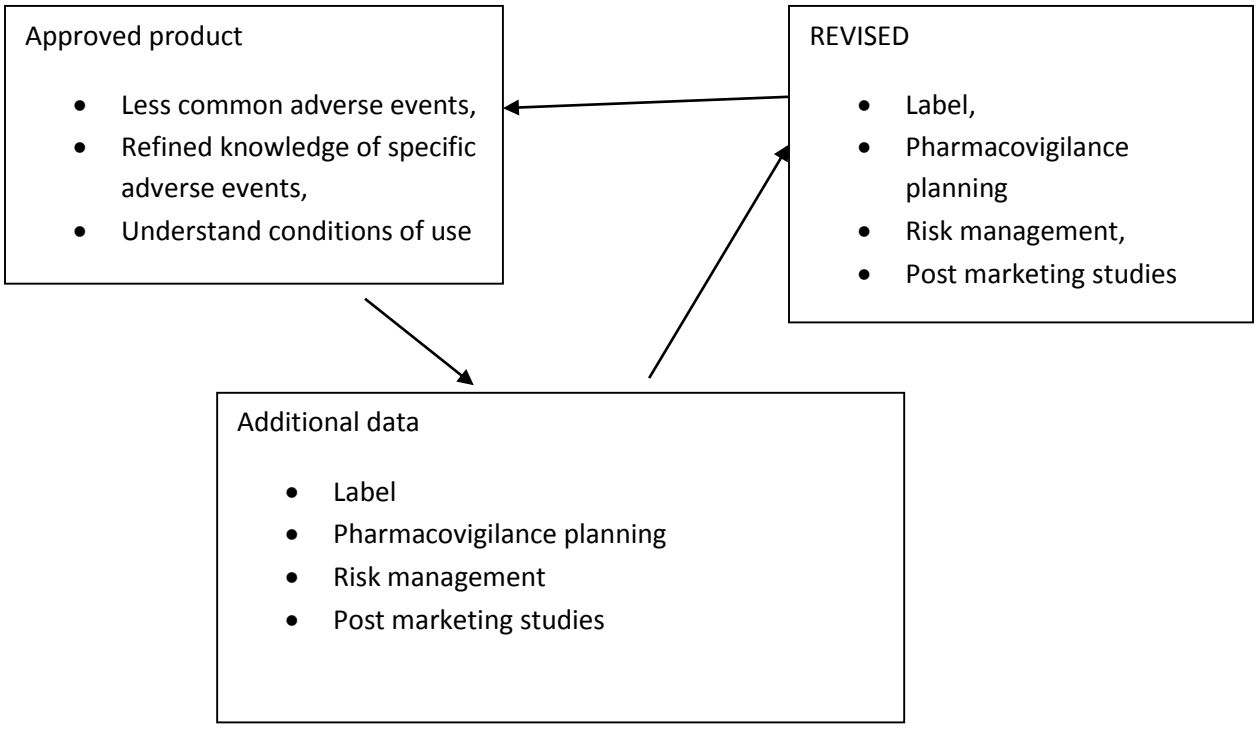
Toxicity and safety studies are done at pre-clinical stage in animals and through the human clinical stage. At this point, knowledge on Common adverse events and signals of other adverse events is obtained.

APPROVAL STAGE

A thorough review of the data accrued from the clinical data forms the basis for product Label, Pharmacovigilance planning and Risk management and Post marketing studies.

POSTMARKETING STAGE

This stage in the product lifecycle aims at obtaining more data as indicated below



Having looked at the source of safety data, so what is the relevance of reporting adverse drug reactions and drug related problems? The answer is; to learn about new risks, Learn more about known risks, Learn about medication errors and Learn about product defects. This new information is important because it can enable;

- The patients and practitioners to make informed choices
- patients to use medicines properly, effectively, and safely
- patients and practitioners to monitor treatment both for effectiveness and the development of adverse drug reactions
- health authorities s and practitioners to modify treatment as needed
- Manufacturers and regulators to make changes to product labels and, if needed, to marketing authorization status.

A CASE OF WHAT PHARMACOVIGILANCE CAN DO

Natalizumab – An Example of What Pharmacovigilance Can Do.

Natalizumab is an Integrin receptor antagonist which binds to α4-subunit of α4β1 and α4β7 integrins. Initially it was approved (23 November 2004) in the USA to reduce frequency of clinical exacerbations in patients with relapsing form of multiple sclerosis.

Within three months of approval, two cases of progressive multifocal leukoencephalopathy (PML) was reported in multiple sclerosis patients through Routine Pharmacovigilance reporting system.(PML is a rare, serious, progressive neurologic disease, usually occurring in immunosuppressed patients, often resulting in irreversible neurologic deterioration and death). Marketing was suspended and Intensive evaluation of all data was done.

Intensive evaluation revealed no additional cases in multiple sclerosis patients. FDA sought input from experts and the public, including patients. Marketing was resumed on 05 June 2006 with **strict risk management**, restricted **distribution** and **registry of all patients**

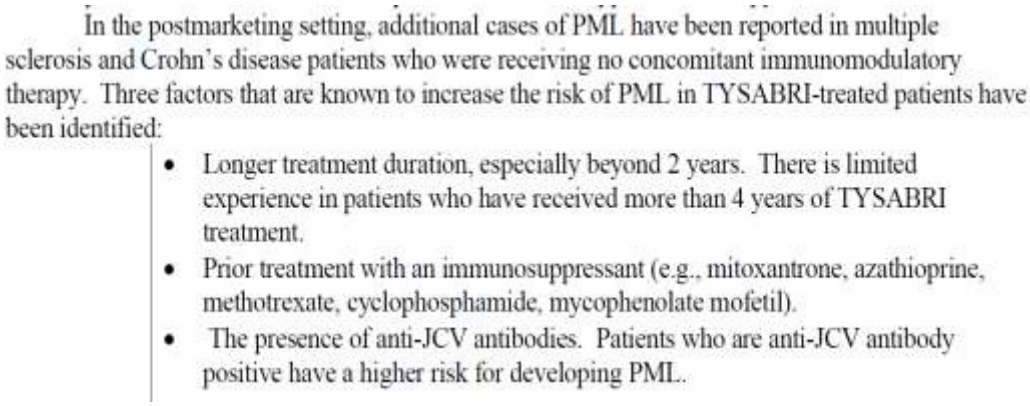
Following continuous risk management and monitoring of the product, more information was obtained as indicate below.

[In the post marketing setting, additional cases of PML have been reported in multiple sclerosis patients who were receiving no concomitant immunnomodulatory therapy. In patients treated with TYSABRI, the risk of developing PML increases with longer treatment duration, and for patients treated for 24 to 36 months is generally similar to the rates seen in clinical trials. There is limited experience beyond 3 years of treatment. There are no known interventions that can reliably prevent PML or adequately treat PML if it occurs. It is not known whether early detection of PML and discontinuation of TYSABRI will

mitigate the disease.The risk of PML is also increased in patients who have been treated with an immunosuppressant(not including prior treatment with short courses of corticosteroids) prior to receiving TYSABRI]

Courtesy of Gerald J. Dal Pan, MD, US FDA

Assessment of the information led to the revision of the product label (Label updated in February 2010)to include duration of treatment as a risk factor for PML based on 31 cases of PML in about 66,000 treated patients label updated in April 2011 to include prior immunosuppression as a risk factor for PML based on 102 cases of PML in about 82,732 treated patients



In the postmarketing setting, additional cases of PML have been reported in multiple sclerosis and Crohn's disease patients who were receiving no concomitant immunomodulatory therapy. Three factors that are known to increase the risk of PML in TYSABRI-treated patients have been identified:

- Longer treatment duration, especially beyond 2 years. There is limited experience in patients who have received more than 4 years of TYSABRI treatment.
- Prior treatment with an immunosuppressant (e.g., mitoxantrone, azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil).
- The presence of anti-JCV antibodies. Patients who are anti-JCV antibody positive have a higher risk for developing PML.

Courtesy of Gerald J. Dal Pan, MD, USFDA

Label updated in January 2012 to include antibodies to JC virus as a risk factor for PML based on 201 cases of PML in about 96,582 treated patients.

Conclusion

Risks of medicines arise from intrinsic pharmacological properties, Product defects, how medicines are used and these vary from place to place.

Monitoring and Spontaneous Reporting of adverse events can be used for making Regulatory Decisions. Spontaneous reports are one of the most frequent sources of data for post approval regulatory actions.

The specific actions depend on the national or regional regulatory system and the most frequent action is some sort of change to the safety portion of the product label.

The National Pharmacovigilance Centre introduces e-Reporting of Adverse Events in Uganda.

Since inception of the National Pharmacovigilance Centre, suspected adverse drug reaction reports and reports on many other drug related problems have been received mainly from health care professional using the national reporting form. One of the challenges faced by the use of the reporting form is the delay in relaying information from the reporter to the national centre. The delay could mostly hamper timely assessment and feedback on the suspect adverse event especially if it is of serious nature.

The National pharmacovigilance centre has made a stride to introduce an electronic reporting system which will be used by both patients and health workers to report adverse event is a timely manner.

The centre hopes that by this new development, there will be an increase in the reporting rates since both consumers and health providers will be able to report easily and the information will be assessed in a timely manner to aid identification of possible signals. More updates will follow in the next issue of this bulletin.

REPORTING FROM THE ANNUAL INTERNATIONAL PHARMACOVIGILANCE MEETING

Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem. PV is increasingly gaining significance in pursuit of safe-guarding public health.

The Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring is hosted annually by one of the Member countries which provide a platform for Member Countries to discuss current issues and concerns in pharmacovigilance in confidential and collegial atmosphere.
The 38th Annual meeting was held on 3$^{rd\ to\ 6th}$ November 2015 and hosted jointly by Indian Pharmacopoeia Commission (IPC), National Coordinating Centre- Pharmacovigilance Programme of India (NCC-PvPI), and WHO.
The meeting objective was to facilitate partnerships among WHO participating countries in Pharmacovigilance, including national pharmacovigilance centres, industry and research institutions, to transfer and demonstrate efficient methodologies to showcase best practices of Pharmacovigilance for integrated safety data management, knowledge and information sharing and step towards ensuring safety of medicines through strengthening bilateral and multilateral partnerships.

Meeting highlights

During the meeting, the following areas were key discussion points.

1. Effective communication in pharmacovigilance as an important aspect. This involves "telling a story' in order to cause a change. The communication must encourage reporting, explain what and why pharmacovigilance is done and to provide timely relevant information on medicine safety issues.
2. Building a Global Safety Culture.
   Pharmacovigilance is global in a sense that there are some commonalities to drug risks around the world and we can all learn from each other. However Pharmacovigilance is also Global" referring to the "whole of a medication use system," which is local. Pharmacovigilance should therefore be used as a tool to monitor and evaluate medicine use for post approval regulatory actions by countries. This process is iterative, incremental and essential for building a Global Safety Culture
3. Use of the state of art reporting system, high technology systems for analysis of information. Development of patient/reporter friendly reporting technologies like E-reporting was discussed as important in pharmacovigilance
4. Sharing global information during a medicinal product-related crisis. Having a crisis management plan is important for countries to adopt.
5. Evaluating benefit / risk assessment in drug regulatory decisions: adapting international decisions to local settings was observed to be important.
6. Need to strengthen pharmacovigilance in public health programs. The need to quickly provide patients with therapies for resistant TB and HIV underpins the need to have strategies for monitoring safety of these new therapies.

The future of Pharmacovigilance.

In ten years, what can we tell our children and grandchildren that we achieved? This question posed led to developing of several aspects (VISION) that will drive the future of PV.

- PV as a broad field of action, covering multiple concerns, involving many partners committed to all aspects of patient safety
- PV integrated into all aspects of healthcare, incorporated into medical systems and including risk factors for patients
- PV education for everyone is routine
- PV underpinned by robust, enabling legislation and regulation in all countries
- PV and safety reporting familiar and understood by the whole population; empowered, autonomous patients

- Rational prescribing rules the day
- Preventable ADRs and medication errors are very rare
- The language of PV for all audiences is simple, appropriate and sensitive
- PV is cost-effective and the social and financial arguments about lives saved and other benefits are well developed and promoted
- PV is responsive and smart, not least in emergency situations
- PV is live and active in communities
- PV has mastered and exploited the best of modern media and technology to serve the health and welfare of the people

National case report(s)

STEROID- INDUCED DIABETES: CASE REPORT

Compiled by Sharon and Victoria Nambasa

M.J, an adult male had a successful eye operation (lens transplant) from a private hospital in kampalain2015.On discharge; he was prescribed three eye drops, all consisting of steroids as well as oral medication, which included prednisolone 5mg tablets, to be taken for five weeks. The dose of prednisolone was tapered over the subsequent weeks with reductions of 10mg each week starting with 50mg once daily in the first week and ending with 10mg each week and ending with 10mg once daily in the fifth week. Despite the tapering plan, the patient observed a gradual rise in blood glucose levels during the first and second weeks of drug use. He was previously diagnosed with diabetes a few years back although the condition was well controlled with diet restriction, as the oral hypoglycemic had been withdrawn. Before the operation, his blood sugar was between 72- 110mg/dl. A week after the ope ration, he reported experiencing the cardinal signs of hyperglycemia (polyuria, polydipsia and unexplained weight lose). On returning to the hospital, prednisolone was withdrawn along with two eye drops leaving Tobradex®eyedrop. He was then prescribed Metformin 500mg twice daily for three days however no change was observed; Metformin was increased to 1gm twice daily which was futile. Pioglitazone was added to the regimen and still unresponsive. The condition became alarming to the health workers and they later decided to give him a regimen consisting of three drugs namely:- Glucophage 1gm twice daily; Pioglitazone 30mg once daily and Glimepiride 2mg once daily. After two weeks of use, his blood glucose levels lowered and stabilized, and he is still managed on the 3-drug regimen.

Editorial comment

With unavoidable use of steroids (particularly corticosteroids) in treatment of people with pre-existing diabetes, undoubtedly monitoring of hyperglyceamia is critical. This may be termed steroid- induced hyperglycemia which at times is an iatrogenic form of Type 2 Diabetes Mellitus. Cortical steroid administration is known to modulate carbohydrate Metabolism via complex mechanisms, including effects on insulin receptors in liver, muscle and adipose tissue. These effects promote hyperglycemia in “at risk” individuals Glucose

levels in most individuals are predicted to rise approximately following administration of oral steroids and sooner following administration of intravenous steroids. Capillary Blood Glucose (CBG) monitoring is paramount to guiding appropriate therapeutic interventions.

The recommended target level for glucose in hospital practice is 6-10mmol/l. The dose and duration of steroid are essential in diagnosis since it is more likely if the doses are high; the glucocorticoid is more potent (Prednisolone and dexamethasone being the usual culprits) and the duration of therapy is long. This is aided by the presence of the clinical signs (such polyuria and polydipsia.

The mainstay of treatment is Insulin therapy following discontinuation of the corticosteroid. Insulin has the great advantage of being almost infinitely titratable and significantly more potent than any other currently available hypoglycemic.

All the major classes of oral Hypoglycemic Agents (metformin, sulphonylureas and thiazolidinedione's) can be used but unless the dose of corticosteroid used is relatively low e.g.: 5-20mg once daily of prednisolone; these alone are rarely adequate.

In addition, topical corticosteroids are perceived to have minimal or no effect on blood glucose which is absolutely false. Multiple studies have shown that topically applied high- and ultra- high potency corticosteroids can be absorbed well enough to cause systemic side effects. (Medscape, January, 21, 2009).

Even over-the-counter low-potency ointments that contain hydrocortisone, when used regularly and for longer than several months, may include a blood glucose effect.

Conclusion and Recommendations:

Corticosteroids are essential in the management of variety of conditions; post-operative and out- patient; however health practitioners should be aware of their potential and at times life threatening effect on blood glucose in diabetic patients and " at risk" individuals.

It is therefore advised that continuous use of low-potency to high-potency oral/topical/steroids not exceed 3 months. Patients should be closely monitored with

continuous measurements of their blood sugar levels, and as well, encouraged to consult/inform their prescribing physicians if they are experiencing increment.

Global safety updates

Ibuprofen

Small increased cardiovascular risk with daily doses at or above 2,400mg

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) commonly used for the reduction of pain, inflammation and fever.

The most recent by regulatory body in European agency has confirmed a small increase in the risk of arterial thrombotic events (e.g. myocardial infraction or stroke) in patients taking high doses of ibuprofen (at or above 2,400/day).

The advised to health- care professionals is that:

- Ibuprofen should be prescribed at the lowest dose for the shortest duration possible.
- Patients with uncontrolled hypertension, congestive heart failure (NYHA 11-111), established ischemic heart disease, and/or cerebrovascular disease should only be treated with ibuprofen after careful consideration and high doses (2400 mg/day) should be avoided.
- Careful consideration should also be exercised before initiating long-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, and smoking), particularly if high doses of ibuprofen (2400 mg/day) are required.
- Reference:
    - Drug Safety Newsletter, HPRA, JUNE 2015
    - (See WHO Pharmaceuticals Newsletter No.3, 2015 for Risk of serious heart and stroke adverse events at high doses in Canada)

Influenza HA vaccine

Risk of optic neuritis

Influenza HA vaccine is used in the prophylaxis of influenza.t cases of optic neuritis have been reported in persons injected with influenza HA vaccine in Japan.Based on expert advice and available evidence; it is recommended the risk of optic neuritis should be considered with “Encephalitis/encephalopathy and myelitis” as “clinically significant adverse reactions”.

- Reference:,
- MHLW/PMDA, 7 July 2015(www.pmda.go.jp/english/)

Methylprednisolone (intravenous injection)

Risk of Liver injury

- Methylprednisolone is a corticosteroid drug typically used for its anti-inflammatory effects. Administration into a vein (intravenous) is generally only used for short periods in severe inflammatory conditions.
- A safety review was initiated following the identification of 28 published international cases of liver injury associated with intravenous methylprednisolone, four of which had a fatal outcome.
- Up until December 31, 2013, three Canadian reports were received and only one case of liver injury was possibly associated with intravenous methylprednisolone.
- Among the 28 cases identified in the literature, the time to onset of the liver injury varied from several days to several months. Of these cases, 27 were considered severe, and death was reported in four cases. Patients’ signs and symptoms of liver injury reappeared in almost half of the cases. Health Canada has announced that evidence of an intravenous methylprednisolone and the occurrence of liver injury with a variable time to onset. The prescribing information for solu-medro ® and solu-medrol® and solu-medrolact-o-vials® have been updated to reflect the available evidence regarding the risk of liver injury. Manufacturers of generic versions of this drug will also be asked to update their product information.

Reference:

Summary Safety Review,Health Canada, 18 June 2015(www.hc-sc.gc.ca)

Tramadol Hydrochloride

Risk of respiratory depression

Tramadol is used for relief of pain but cases associated with respiratory depression have been reported in patients treated with tramadol hydrochloride

Among the reports on tramadol hydrochloride received at the Uganda national pharmacovigilance centre, respiratory depression is not among the reactions .However based on advice and available evidence from various literature Patients should be carefully monitored for Respiratory depression . If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Reference:

www.pmda.go.jp/english/

WHO Pharmaceuticals Newsletter no.4 2015

Technetium (99m Tc)Hydroxymethylenediphosphonate injection

Risk of shock and anaphylaxis

Technetium (99m Tc) hydroxymethylenediphosphonate is used as a diagnostic agent for bone diseases with scintigraphic imaging of the bone.cases of shock and anaphylaxis have been reported in patients treated with products in Japan.

CAUTION SHOULD BE TAKEN FOR patients with a history of hypersensitivity to any ingredients of this product . Patients should be carefully monitored. If any abnormalities such as dyspnoea, decreased blood pressure, rash, etc. are observed, appropriate measures (www.pmda.go.jp/english/)

Nonsteroidal Anti-Inflammatory (NSAIDs)

Increased chance of heart attack or stroke

The US FDA has announced the strengthening of the existing label warnings of non-aspirin NSAIDs for increased risk of heart attack or stroke. Based on the FDAs comprehensive review

of new safety information, the FDA has requested updates to the drug labels of all prescription NSAIDs. The FDA will also request updates to the over-the-counter (OTC) non-aspirin NSAID Drug Facts labels.

- Prescription NSAID labels will be revised to reflect the following information:
- The risk of heart attack or stroke can occur as the first weeks of using an NSAID. The risk may increase with longer use of NSAID.
- The risk appears greater at higher doses.
- It was previously thought that all NSAIDs may have a similar risk. Newer information makes it less clear that the risk for heart attack or stroke is similar for all NSAIDs; however, this newer information is not sufficient for us to determine that the risk of any p
- NSAIDs can increase the risk of heart attack or stroke in patients with without heart disease or risk factors for heart disease. A large number of studies support this finding, with varying estimates of how much the risk is increased, depending on the drugs and the doses studied.
- In general, patients with heart disease or risk factors for it have a greater likelihood of heart attack or stroke following NSAID use than patients without this risk at baseline.
- Patients treated with NSAIDs following a first heart attack were more likely to die in the first year after the heart attack compared to patients who were not treated with NSAIDs after their first heart attack.
- There is an increased risk of heart failure with NSAID use.

Reference:

- Drug Safety Communication, US FDA, 9 July 2015(www. Fda.gov)

For more information and comments, please contact

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