World Health Organization

WHO Pharmaceuticals NEWSLETTER

2017

No. 1

WHO Vision for Medicines Safety

No country left behind: worldwide pharmacovigilance for safer medicines, safer patients

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of national pharmacovigilance centres and other sources such as specialized bulletins and journals, as well as partners in WHO.

The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

Safety and Vigilance: Medicines,

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This Newsletter is also available at:
http://www.who.int/medicines

The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities around the world. It also provides signals based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

This newsletter includes three feature articles describing: Introduction of an electronic system for reporting adverse drug reactions in Tanzania, Third WHO Asia Pacific Pharmacovigilance Training Course, and Recommendations from the 39th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

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Suggested citation. WHO Pharmaceuticals Newsletter No.1, 2017: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Printed in Switzerland

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Amiodarone (intravenous)

Risk of adverse effects of the heart in newborns

Canada. Health Canada has requested manufacturers to update the product information for intravenous amiodarone products to include heart risks in new-borns. Although this information is already mentioned for adult patients, it is important that health-care professionals recognize potential risks in newborns and infants.

Amiodarone is used to treat arrhythmias in adults. It is also prescribed by some doctors for the treatment of life-threatening arrhythmias in foetuses and newborns when other medications have not worked.

Health Canada reviewed the potential risk of adverse effects in foetuses and newborns with intravenous amiodarone following an update of product label in the United States which included warnings about potential effects on the heart, nervous system and development and growth of foetuses and newborns.

At the time of the review, Health Canada received three Canadian reports and retrieved 12 additional reports from the published literature of serious adverse effects of the heart including potentially fatal heart attacks in new-borns who received amiodarone for life-threatening abnormal heart rhythms. In 13 of the 15 reports reviewed, it was determined that amiodarone may have played a role in the development of adverse effects.

Results of a published study investigating amiodarone use in children suggested that the risk of hypotension, bradycardia and atrioventricular block may be greater in children than in adults exposed to amiodarone.

Hypothyroidism can be caused by amiodarone exposure *in utero* and is a known cause of developmental delays (such as in learning, speech, and movement) if untreated. However, some children have had developmental delays following amiodarone exposure despite having normal levels of thyroid hormone.

Health Canada's review of the available information did not establish a link between the use of amiodarone during pregnancy and the risk of developmental delays in new-borns but did find a possible link to adverse effects on the heart.

Reference:
Summary Safety Review, Health Canada, 6 January 2017 (*www.hc-sc.gc.ca*)

Bisphosphonates (intravenous)

Risk of osteonecrosis of the jaw

Canada. Health Canada has worked with manufacturers to update safety information of intravenous bisphosphonates products (pamidronate, Zometa®; zoledronate, Aclasta®, clodronate disodium) to reflect the risk of osteonecrosis of the jaw, and to mention the additional factors that may play a role in jaw bone loss for all bisphosphonate products.

Bisphosphonates are used to strengthen bones in a variety of bone-related diseases, such as: osteoporosis; Paget's disease; bone metastases; hypercalcaemia of malignancy; and certain cancers.

There are different kinds of bisphosphonate formulations that can be used orally and/or intravenously.

Health Canada reviewed the potential risk factors of osteonecrosis of the jaw with bisphosphonate use in light of updates to the European product safety information for injectable bisphosphonates.

At the time of the review, Health Canada received 125 unique Canadian reports of jaw bone loss associated with the use of bisphosphonate products. Jaw bone loss was commonly reported in cancer patients.

A review of recent publications and an analysis of the Canadian reports above showed a higher risk of jaw bone loss with the use of bisphosphonates, especially when IV formulations are used compared to oral formulations. Higher doses and strengths as well as longer treatment periods also contribute to the risk.

This review also found other risk factors for jaw bone loss including dental conditions and procedures, radiation therapy, and medical conditions such as anaemia or coagulopathies.

At the time of the review the product information for all bisphosphonates already included a warning about the risk of jaw bone loss, but there were differences in the way the risk was described for the different medicines in this class.

Health Canada's review confirmed the known risk of jaw bone loss with bisphosphonate product use, and further concluded that this risk is higher with intravenous bisphosphonate products, especially in cancer patients.

Reference:
Summary Safety Review, Health Canada, 25 November 2016 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletters No.4, 2016: Risk of osteonecrosis of external auditory canal in Japan and No1, 2016: Risk of osteonecrosis of the external auditory canal in the United Kingdom)

Bupropion and varenicline

Revision of mental health adverse effects

USA. The US Food and Drug Administration (FDA) has

announced that the Boxed Warning for serious mental health adverse effects has been removed from varenicline (Chantix®) product label. Also, the language describing the serious mental health adverse effects seen in patients quitting smoking has been removed from the Boxed Warning in bupropion (Zyban®) label. These updates are based on the results from a review of a large clinical trial which indicate that although the risk of these mental health adverse effects is still present, it is lower than previously suspected.

Bupropion and varenicline are medications used as an aid to smoking cessation treatment.

The FDA has determined that the risk of serious adverse effects on mood, behaviour, or thinking with varenicline and bupropion is lower than previously suspected. The risk of these mental health adverse effects is still present, especially in those currently being treated for mental illnesses such as depression, anxiety disorders, or schizophrenia, or who have been treated for mental illnesses in the past. However, most people who had these adverse effects did not have serious consequences such as hospitalization. The results of the trial confirm that the benefits of stopping smoking outweigh the risks of these medicines.

The FDA review of the clinical trial results has also confirmed that bupropion, varenicline, and nicotine replacement patches were all more effective for helping people quit smoking than placebo. These medicines were found to better help people quit smoking regardless of whether or not they had a history of mental illness.

The patient medication guide that explains the risks associated with the use of the medicines will continue to be provided with every patient prescription; however, the risk evaluation and mitigation strategy (REMS) that formally required the Medication Guide will be removed.

Reference:
Drug Safety Communication, US FDA, 16 December 2016 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletter No.1, 2016: Risk of psychiatric symptoms by drug-alcohol interaction in Australia)

Cajeput Oil (*Melaleuca leucodendran*)

Risk of glottal spasm and bronchospasm

Malaysia: The National Pharmaceutical Regulatory Agency (NPRA) has updated package inserts for cajeput oil containing products to provide information on the risk of glottal spasm and bronchospasm.

Cajeput oil is an essential oil derived from a plant called Kayu Putih (*Melaleuca leucodendran*). It is traditionally used to provide relief of muscle pain, muscle cramps, muscle strains and abdominal discomfort. It is commonly used in infants and small children during post-natal care to provide relief of bloating or abdominal distension, as well as to give warmth after a bath.

From year 2001 to August 2015, the NPRA has received four ADR reports associated with the use of cajeput oil-containing products, all of which involved children aged between eight days to 14 months.

Three of the reports documented three skin adverse drug reactions, namely contact dermatitis, papular rash, and skin hyperpigmentation. One report involved accidental ingestion, in which the patient experienced vomiting.

A literature review has shown that there are warnings of adverse reactions such as glottal spasm, bronchospasm or even asthma-like attacks in paediatric patients when cajeput oil is applied on the face. This could result in breathing difficulties in infants and small children.

The NPRA has advised that preparations containing the oil should not be applied to the faces of infants or small children, as glottal spasm might occur.

Reference:
MADRAC Newsletter, National Pharmaceutical Regulatory Agency (NPRA), Malaysia, Vol. 20 August 2016 *(http://npra.moh.gov.my/)*

Cobicistat, ritonavir and corticosteroid metabolised by CYP3A

Risk of adrenal suppression due to a pharmacokinetic interaction.

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has strengthened the product information for cobicistat-containing products to warn of the potential interaction with coticosteroids, resulting in systemic corticosteroid-related adverse effects.

Cobicistat is a HIV-treatment-boosting agent and ritonavir is a HIV-protease inhibitor to treat HIV/AIDS.

An EU-wide review has identified eight cases worldwide (including one published report) of adrenal suppression during treatment with a cobicistat-containing regimen (Stribild®) and a subsequent prescription of an inhaled, intranasal, or intra-articular corticosteroid.

Reported adverse reactions were adrenal insufficiency, adrenal suppression and Cushing's syndrome. The corticosteroids involved were intranasal and inhaled

fluticasone, oral budesonide, and intra-articular triamcinolone. From clinical trials, a further report of adrenal insufficiency was identified where epidural methylprednisolone had been used together with intranasal fluticasone.

Up until 21 November 2016, 26 UK Yellow Card reports of an interaction with triamcinolone and ritonavir have been reported: 18 reactions of Cushing's syndrome or cushingoid features, and 17 of adrenal suppression. A separate EU review identified two reports of Cushing's syndrome from interactions between ocular dexamethasone and ritonavir. The review also noted an increased risk of systemic adrenal effects occurring with both ocular and cutaneous use after intensive or long-term therapy, and which were considered to be risk factors for interactions with ritonavir.

The MHRA has highlighted the need: for monitoring patients for adverse events in patients using a corticosteroid metabolised by cytochrome P450 3A (CYP3A) and a HIV-treatment-boosting agent; to consider if the potential benefit to the patient outweighs the risk; and to use lower-risk alternative corticosteroids where possible (particularly, inhaled or intranasal beclomethasone).

Reference:
Drug Safety Update, MHRA, Volume 10, issue 5:1, December 2016 *(www.gov.uk/mhra)*

(See WHO Pharmaceuticals Newsletter No.6, 2016: Potential drug interaction: increased risk of systemic corticosteroid effects with Cobicistat containing products and corticosteroids primarily metabolised by CYP3A in Ireland)

Codeine-containing products

Restrictions on use in children and adolescents due to respiratory adverse events

Singapore. The Health Sciences Authority (HSA) has worked with marketing authorization holders to update the package inserts of codeine-containing products to include the restriction of the use in children and adolescents.

Codeine is used for the treatment of pain and the relief of cough and cold. It is available in various dosage forms such as tablets, syrups and injections.

The HSA first issued an interim safety update in 2014 to health-care professionals which summarized the overseas recommendations on the use of codeine-containing products for pain relief in paediatric patients. It also informed health-care professionals that the HSA would be conducting a comprehensive review of such products in Singapore for pain relief and for the relief of cough symptoms in children. Subsequently, a Dear Health-care Professional Letter was issued in July 2016 regarding new restrictions on the use of codeine-containing products in order to reduce the risk of death and respiratory depression in infants and children.

To date, the HSA has received five reports of respiratory adverse events (AE) such as dyspnoea and bronchospasm in children between nine to 16-years of age associated with the use of codeine-containing cough products in Singapore. No deaths or cases of severe respiratory depression have been reported in Singapore.

Taking into consideration the current available scientific evidence, input from clinical experts in Singapore, local and international AE reports, the potential for serious and fatal AEs, Singapore population and international regulatory actions, the HSA has reviewed the benefits versus the risks of codeine and recommended the restrictions on the use of codeine-containing products in children and adolescents in Singapore. It is recommended that use is restricted in indications such as post-operative pain following surgical procedures, unproductive coughs, and caution is taken when used in children with underlying respiratory conditions.

Reference:
Product Safety Alerts, HSA, 20 December 2016 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletters No.6 and No.1 in 2016, No.4 and No.3 in 2015, No.5 and No.4 in 2013, and No.5 in 2012 for related information)

Combined hormonal contraceptives

Risk of venous and arterial thromboembolism

Australia. The Therapeutic Goods Administration (TGA) has recommended that the Product Information and Consumer Medicine Information documents for combined hormonal contraceptives (CHCs) should be updated to ensure clearer and more consistent information is provided across products.

A review conducted by the TGA found that while the risk of venous thromboembolism (VTE), such as deep vein thrombosis and pulmonary embolism for women, is generally rare, the risk was slightly increased for women using combined hormonal contraceptives (CHCs).

The review also found that, based on currently available data, the increase in risk of VTE varied according to the progestogen included in the CHC. The risk of arterial

thromboembolism (ATE), such as myocardial infarction or stroke, is also increased with the use of CHCs, however, it is still very rare, and there is no evidence for differences in risk between CHCs.

The TGA has advised that health-care professionals should note the risk of venous thromboembolism is increased in women taking a combined hormonal contraceptive containing ethinyloestradiol and a progestogen and that, based on current data, the risk varies according to the progestogen used. The risk of arterial thromboembolism is also increased, however, there is currently no evidence that risk varies according to the progestogen used.

Reference:
Medicines Safety Update, TGA, Vol. 7, No. 5, October-December 2016 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletters No.4 in 2015, No.6 and No.4 in 2013 for related information)

Direct-acting antivirals for hepatitis C treatment

Potential risk of hepatitis B virus reactivation

1. Canada. Health Canada has recommended that the safety information for all direct-acting antivirals (DAAs) should be updated to include the risk of hepatitis B reactivation. In addition, an Information Update will be published to further inform health-care professionals.

DAAs (daclatasvir (Daklinza®), dasabuvir (Exviera®), dasabuvir/paritaprevir/ombitasvir (Holkira Pak®), sofosbuvir/ledipasvir (Harvoni®), simeprevir (Olysio® and Galexos®), sofosbuvir (Sovaldi®), ombitasvir/paritaprevir/ritonavir (Viekirax® and Technivie®), sofosbuvir/velpatasvir (Epclusa®), asunaprevir (Sunvepra®) and elbasvir/grazoprevir (Zepatier®)) are prescription medicines used to treat chronic HCV infection in adult patients.

Health Canada carried out a safety review following reports of HBV reactivation in patients infected with both HBV and HCV treated with DAAs.

At the time of the review, Health Canada had not received any Canadian reports of HBV reactivation related to DAA use in patients infected with both HBV and HCV.

A total of 13 international reports of HBV reactivation were retrieved from different sources. Of these, 12 reports were considered to be possibly related to the use of DAAs: 11 reports reported the use of sofosbuvir or products with sofosbuvir and ledipasvir; one reported daclatasvir use. Of the 13 reports one could not be reviewed further because it did not provide enough information. Three of the 13 reports described symptoms of moderate HBV reactivation. One of the cases reported severe HBV reactivation resulting in liver failure and the patient needed a liver transplant.

Two studies of the use of DAAs in patients infected with both HCV and HBV reported an increase in viral genes (HBV DNA) in some of the patients. This could lead to reactivation of the HBV infection.

Health Canada's review concluded that there is a potential risk of HBV reactivation in patients co-infected with both HBV and HCV, and the use of DAAs.

Reference:
Summary Safety Review, Health Canada, 1 December 2016 (*www.hc-sc.gc.ca*)

2. EU. The European Medicines Agency (EMA) has confirmed its recommendation to screen all patients for hepatitis B before starting treatment with DAAs; patients infected with both hepatitis B and C viruses must be monitored and managed according to current clinical guidelines. These measures aim to minimize the risk of hepatitis B reactivation with DAAs.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) carried out a review of DAAs. It looked into cases of returning signs and symptoms of previously inactive hepatitis B infection (re-activation) when patients were treated with DAAs for hepatitis C.

The PRAC recommendation to include a warning in the prescribing information about hepatitis B reactivation and how to minimize it, has now been endorsed by EMA's Committee for Medicinal Products for Human Use (CHMP).

In addition to data on hepatitis B reactivation, EMA also reviewed data suggesting that patients treated with DAAs who have previously been treated for liver cancer could be at risk of their cancer returning early. The CHMP agreed that companies should carry out a study to evaluate the risk of liver cancer returning with DAAs. In this context, further research is also needed on the risk of new liver cancers in patients with chronic hepatitis C and cirrhosis (liver scarring) that are treated with DAAs.

Reference:
Press release, EMA, 16 December 2016 *(www.ema.europa.eu)*

(See WHO Pharmaceuticals Newsletters No.6, 2016: Risk of hepatitis B reactivation in the US and No.3, 2016: Risk of reactivation of hepatitis B virus in Japan)

Duloxetine, venlafaxine and milnacipran

Prohibition on operating hazardous machine eased

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for duloxetine (Cymbalta®), venlafaxine (Effexor®) and milnacipran (Toledomin®) have been updated to ease the prohibition of operating hazardous machines such as driving a car.

Duloxetine, venlafaxine and milnacipran are serotonin-noradrenaline reuptake inhibitors (SNRIs) used for the treatment of depression/depressed states.

The MHLW/PMDA have investigated the safety of SNRIs on driving or operating other hazardous machinery following a request from the Japanese Society of Neuropsychopharmacology and Japanese Society of Mood Disorders.

Evidence from clinical trials and the literature does not suggest that SNRIs reduce driving performance compared to placebo. Comparison of their safety profiles with selective serotonin reuptake inhibitors (SSRIs) did not show a greater number of accumulated reports of adverse drug reactions that could affect driving, and pharmacologically, no major differences in affinity to receptors relating to "dizziness," "sedation," or "sleepiness" were found. Therefore PMDA has considered that aligning the precautions for SNRIs relating to driving or operating other machinery with the precautions for SSRIs would broaden treatment options and provide proper treatment to patients, and prevent the aggravation of symptoms and recurrences.

Although there are no cases where the involvement of SNRI is clearly present, there have been reports of consciousness disturbance related events that may affect driving without patients themselves noticing signs of the event based on the accumulated adverse drug reaction reports in Japan. Accordingly, the PMDA considered when the precautions on patients receiving SNRIs driving or operating other machinery are revised, the prescribing physician and health-care providers must observe the patient's condition carefully, and alert the patient to ensure that the necessary care is taken while driving and that the patient does not drive if he or she experiences adverse drug reactions such as dizziness or somnolence.

Based on the above, the MHLW/PMDA have concluded that it is appropriate to revise the precautions for driving to the description similar to the precautions of SSRIs, rather than the uniform prohibition of operating hazardous machinery including driving while receiving a SNRI.

Reference:
Revision of Precautions, MHLW/PMDA, 25 November 2016 *(www.pmda.go.jp/english/)*

Fluoroquinolones

Risk of retinal detachment

Singapore. The HSA, has worked with marketing authorization holders to update the package inserts of fluoroquinolone-containing products (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, pefloxacin, ofloxacin, and lomefloxacin) to warn of the potential risk of retinal detachment. The need to seek medical attention in the event of visual impairment and disturbances with these products has been highlighted.

Fluoroquinolones are broad-spectrum antibiotics that are used to treat a wide range of indications such as the infections of the urinary tract, respiratory tract, skin and soft tissue, bones and joints, and abdominal cavity.

The association between oral fluoroquinolones intake and occurrence of retinal detachment has been investigated in several epidemiological studies. Two large cohort studies have found a statistically significant increased risk of retinal detachment with use of oral fluoroquinolones.

The increase in risk of retinal detachment was not confirmed in other published studies as well as in a study conducted by the EMA. However, in most of these studies, the confidence intervals of the calculated risks were relatively wide, thus a small increase in risk cannot be excluded.

The HSA has not received any reports of retinal detachment associated with the use of fluoroquinolones, but has received several reports describing visual disturbances such as blurred vision, eye redness, itching and conjunctivitis.

Since retinal detachment is serious and its association with oral fluoroquinolones use cannot be ruled out, the HSA has advised that health-care professionals should consider this potential risk when prescribing and dispensing fluoroquinolones to patients.

Reference:
Product Safety Alerts, HSA, 20 December 2016 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.1, 2016: Risk of retinal detachment in Canada)

General anaesthetic and sedation drugs

Potential risk of effects on development of children's brains

USA. The US FDA has requested that warnings are added to the labels of general anaesthetic and sedation drugs (desflurane, etomidate, halothane, isoflurane, ketamine, lorazepam, methohexital, midazolam, pentobarbital, propofol, sevoflurane) to inform the public about the potential effect on the development of children's brain if used in children under three years or in pregnant women during the third trimester.

Anaesthetic and sedation drugs are necessary for infants, children, and pregnant women who require surgery or other painful and stressful procedures. In addition, untreated pain can be harmful to children and their developing nervous systems.

The FDA has warned that repeated or lengthy use of general anaesthetic and sedation drugs during surgeries or procedures in children younger than three years or in pregnant women during their third trimester may affect the development of children's brains.

The FDA has recommended that health-care professionals should balance the benefits of appropriate anaesthesia in young children and pregnant women against the potential risks, especially for procedures that may last longer than three hours or if multiple procedures are required in children under three years.

Reference:
Drug Safety Communication, US FDA, 14 December 2016 *(www.fda.gov)*

Idelalisib

Risk of serious infections

Singapore. The HSA has updated the package insert for idelalisib (Zydelig®) to include warnings of the risk of serious infections. In addition, a Dear Health-care Professional Letter was issued by the company in April 2016 to communicate the safety concerns to health-care professionals.

Idelalisib is approved, in combination with rituximab, for the treatment of relapsed CLL in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities. It is also indicated for the treatment of relapsed follicular B-cell non-Hodgkin lymphoma and relapsed small lymphocytic lymphoma in patients who have received at least two prior systemic therapies, based on overall response rates to idelalisib monotherapy. Idelalisib is not recommended for first-line treatment of chronic lymphocytic leukaemia (CLL).

The marketing authorisation holder reviewed three Phase III clinical trials that showed an increase in the rate of serious adverse events and mortality when idelalisib was added to standard therapies in first-line treatment of CLL and relapsed indolent non-Hodgkin lymphoma (iNHL). The majority of events were infections, which included sepsis and opportunistic infections such as PJP and CMV infections. These trials have since been terminated by the company.

To date, the HSA has not received any reports of serious infections associated with the use of idelalisib in Singapore.

The HSA has advised that health-care professionals should take into consideration the above safety information when prescribing idelalisib and to monitor their patients for signs and symptoms of infections throughout idelalisib treatment.

Reference:
Product Safety Alerts, HSA, 20 December 2016 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletters No.5, No.4, No.3 and No.2 in 2016 for related information)

Iguratimod

Risk of agranulocytosis

Japan. The MHLW and the PMDA have announced that the package inserts for iguratimod (Careram® and Kolbet®) have been updated to include the risk of agranulocytosis as a clinically significant adverse reaction.

Iguratimod is indicated for rheumatoid arthritis.

A total of 10 cases associated with agranulocytosis have been reported in Japan. Of these, a causal relationship could not be excluded in nine cases.

Reference:
Revision of Precautions, MHLW/PMDA, 10 January 2017 *(www.pmda.go.jp/english/)*

Interferon beta-1b

Risk of thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS)

Japan. The MHLW and the PMDA have announced that the package insert for interferon beta-1b (Betaferon®) has been updated to include the risk of thrombotic thrombocytopenic purpura (TTP) and haemolytic uraemic syndrome (HUS) as clinically significant adverse reactions. In addition, the company core datasheet (CCDS) has also been updated by the marketing authorization holder.

Interferon beta-1b is used for prophylaxis of multiple

sclerosis relapse and suppression of progression.

Cases of TTP and HUS have been reported in patients treated with interferon beta-1b both in Japan and overseas. A total of two cases associated with TTP or HUS have been reported in Japan. A causal relationship could not be excluded in both cases.

Reference:
Revision of Precautions, MHLW/PMDA, 10 January 2017 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.1, 2014: Thrombotic microangiopathy by recombinant interferon-beta in the United Kingdom)

Intravenous N-acetylcysteine (NAC) for paracetamol overdose

Reminder of authorised dose regimen; possible need for continued treatment with NAC

The United Kingdom. The MHRA has updated the prescribing information for N-acetylcysteine (NAC) to advise that continued treatment for paracetamol overdose beyond 21 hours may be necessary depending on clinical evaluation of the individual patient, in line with current clinical guidance issued in 2012.

Intravenous NAC is an antidote used to treat paracetamol overdose and is virtually 100% effective in preventing liver damage when given within eight hours of the overdose. After this time, efficacy falls substantially, affording only a very limited window of time in which to successfully prevent serious hepatotoxicity. The authorised posology for NAC is three consecutive intravenous infusions, and continued treatment may be necessary depending on the clinical evaluation of the individual patient.

Since 2012, data for an off-label shortened 2-bag regimen for NAC to treat paracetamol overdose have been published from the Scottish and Newcastle Antiemetic Pre-treatment for paracetamol poisoning (SNAP) study. The Commission on Human Medicines (CHM) has reviewed these findings and also looked at the safety profile of NAC since the 2012 guidance was implemented.

CHM concluded that there was insufficient evidence of efficacy to add information about the off-label shortened 2-bag dose regimen used in the SNAP study to the product information for NAC.

The pattern of potential adverse drug reactions associated with NAC is well established, and no new safety issues have been identified since the 2012 guidance. The authorised NAC product information reflects the safety profile. CHM concluded that the benefits of the authorised 3-bag dose regimen continue to outweigh the risks.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 6:4, January 2017 *(www.gov.uk/mhra)*

Lenalidomide

Risk of reactivation of hepatitis B virus

Japan. The MHLW and the PMDA have announced that the package insert for lenalidomide (Revlimid®) has been updated to include the risk of reactivation of hepatitis B virus as a precaution and a clinically significant adverse reaction.

Lenalidomide is indicated for multiple myeloma and myelodysplastic syndrome associated with a deletion 5q cytogenetic abnormality.

A total of 13 cases associated with reactivation of hepatitis B virus have been reported in Japan. Of these, a causal relationship could not be excluded in four cases.

Reference:
Revision of Precautions, MHLW/PMDA, 10 January 2017 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletters No.5, 2016: Risk of hepatitis B virus reactivation by pomalidomide in Singapore and No.3, 2016: Risk of hepatitis B reactivation by pomalidomide in the United Kingdom)

Levetiracetam

Risk of acute kidney injury

Canada. Health Canada has worked with manufacturers to update the safety information for all levetiracetam-containing products to reflect the potential risk of acute kidney injury, using the same wording as the product brand (Keppra®).

Levetiracetam is a prescription drug used as adjuvant anticonvulsant.

Health Canada reviewed the potential risk of acute kidney injury with the use of levetiracetam, following the publication of an article by the World Health Organization (WHO) that suggested this risk.

At the time of the review, Health Canada had not received any Canadian reports of acute kidney injury related to levetiracetam use.

A search in the WHO Global ICSR database, VigiBase®, found more than 150 international reports of acute kidney injury with the use of levetiracetam. The WHO reviewed 39 of these 150 reports in depth and concluded that levetiracetam had possibly caused acute kidney injury.

In addition, there were six cases of acute kidney injury linked to the use of levetiracetam, published in the scientific literature. While the cases noted other factors such as pre-existing diseases, other medications taken at the same time, or other additional

medical conditions, a link between the use of levetiracetam and acute kidney injury could not be ruled out.

Health Canada's review has concluded that there may be a link between the use of levetiracetam and the risk of acute kidney injury. The current product information for Keppra® informs that cases of acute kidney injury have been reported in patients treated with levetiracetam. Health Canada has requested that the other manufacturers of levetiracetam-containing products also update their product information with the same wording.

Reference:
Summary Safety Review, Health Canada, 6 January 2017 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletter No.4, 2016: Risk of acute renal failure in Japan)

Oral isotretinoin

Potential risk of impotence (erectile dysfunction)

Canada. Health Canada has recommended that the product information for all isotretinoin products (Accutane®, Clarus® and Epuris®) should include erectile dysfunction as an adverse effect. It already appears in the product information for Epuris® but not for the others.

Oral isotretinoin is authorized to treat various skin conditions such as severe acne, chronic eczema and psoriasis.

Health Canada reviewed the potential risk of impotence following the publication of an article in the scientific literature.

At the time of the review, Health Canada had received a total of nine reports of impotence with oral isotretinoin use. There were no relevant Canadian reports for the other oral retinoid products. The cases reported other factors that may have played a role in impotence such as depression, and causality of isotretinoin could not be certain.

The review found 215 international reports of erectile dysfunction with use of retinoids. There were also published cases of oral isotretinoin use leading to impotence.

Health Canada's review of the available information concluded that there may be a link between the use of oral isotretinoin products and the risk of impotence, but could not draw the same conclusion for the other medicines in the class (e.g. other retinoid products such as alitretinoin, tertinoin, acitretin). Health Canada recommended that the product information for all isotretinoin products is made consistent by listing impotence as an adverse effect.

Reference:
Summary Safety Review, Health Canada, 10 January 2017 (*www.hc-sc.gc.ca*)

Pioglitazone-containing medicines

Risk of bladder cancer

USA. The US FDA has updated the product information for pioglitazone-containing medicines (Actos®, Actoplus Met®, Duetact®, Oseni®), to include an additional description of studies to existing warnings, about the increased risk of bladder cancer.

Pioglitazone is approved to improve blood sugar control, along with diet and exercise, in adults with type 2 diabetes.

The FDA has alerted the public about the possible risk of bladder cancer in September 2010 and June 2011 based on interim results from a 10-year epidemiologic study. The FDA changed the labels of pioglitazone-containing medicines in August 2011 to include warnings about this risk, and required the manufacturer to modify and continue the 10-year study.

As a result of an updated review, the FDA has concluded that use of the type 2 diabetes medicine pioglitazone may be linked to an increased risk of bladder cancer.

The FDA has recommended that health-care professionals should not use pioglitazone in patients with active bladder cancer, and should carefully consider the benefits and risks before using pioglitazone in patients with a history of bladder cancer.

Reference:
Drug Safety Communication, US FDA, 12 December 2016 *(www.fda.gov)*

(See WHO Pharmaceuticals Newsletters No.1 in 2014, No.3 in 2012, No.6 and No.4 in 2011 for rerated information)

Riociguat

Contraindicated for use in patients with pulmonary hypertension associated with idiopathic interstitial pneumonia

Malaysia: The NPRA has updated the package insert of riociguat (Adempas®) to include a contraindication for use in patients with pulmonary hypertension associated with idiopathic interstitial pneumonia (PH-IIP). In addition, the product registration holder of riociguat issued a direct health-care professional communication letter.

Riociguat is approved for use in patients with chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH).

The RISE-IIP study was a randomized, double-blind, placebo-controlled, multicentre phase II clinical trial that

investigated the efficacy and safety of riociguat patients with symptomatic PH-IIP. This study was terminated early when preliminary results revealed an increased mortality in patients receiving riociguat (17 deaths) compared to those receiving placebo (four deaths). Serious adverse events, mostly respiratory disease or lung infections, were also reported more frequently in the patient group receiving riociguat compared to placebo group.

An evaluation of the interim results concluded that the benefit-risk balance of riociguat in patients with PH-IIP is negative, and recommended that this information is included in the product information of riociguat as a new contraindication.

At the time of this publication, the NPRA had not received any ADR reports related to this product in Malaysia.

Reference:

MADRAC Newsletter, National Pharmaceutical Regulatory Agency, Malaysia, Vol. 20 August 2016 *(http://npra.moh.gov.my/)*

(See WHO Pharmaceuticals Newsletter No. 5, 2016: Contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias in the United Kingdom)

Risperidone

Revised indication for treatment of dementia

Singapore. The HSA has worked with marketing authorization holders to update the package inserts of risperidone products to include revisions for the indication of use. Risperidone is now restricted for the short-term treatment of persistent aggression in patients with Alzheimer's Dementia (AD) only, and should not be used in other types of dementia, such as mixed/vascular dementia (MD/VD). A Dear Health-care Professional Letter was also issued on 16 June 2016 to advise health-care professionals on these recommendations.

Risperidone is used for the treatment of behavioural disturbances in patients with dementia.

Several other international drug regulatory agencies have similarly restricted the indication of risperidone.

A HSA's benefit-risk assessment on the use of risperidone for the treatment of dementia, was based on current available scientific evidence, expert advice from clinicians in Singapore, safety data submitted by the product licence holder, adverse drug reaction (ADR) reports in Singapore and actions taken by other drug regulatory agencies.

Available data showed that risperidone, at recommended therapeutic doses, demonstrated efficacy in treatment of aggression in elderly patients with moderate to severe dementia (AD, MD or VD).

Cerebrovascular adverse events (CVAE) such as stroke and transient ischemic attack, including fatalities, have been reported in trials of risperidone in elderly patients with dementia-related psychosis. However, the assessment of the post market data showed that there was a higher incidence of CVAE in MD/VD versus AD patients taking risperidone. The HSA has concluded that the benefit-risk profile for use of risperidone in treatment of aggression in dementia remains favourable when it is restricted for the short-term treatment of AD.

Reference:

Product Safety Alerts, HSA, 20 December 2016 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.5, 2015: Risk of cerebrovascular adverse events in patients with vascular or mixed dementia in Australia)

Adrenaline autoinjectors

Single use only

Australia. The TGA has reminded health-care professionals that adrenaline autoinjectors are designed for single use only and should not be disassembled under any circumstances. Health-care professionals are encouraged to ensure that patients and caregivers are also aware of this information to promote the safe use of these medicines.

Adrenaline autoinjectors are indicated for the emergency treatment of anaphylaxis. They are preloaded to deliver an exact dose of adrenaline and include safety features that protect against needle stick injury.

The TGA has been made aware of cases in which first aid providers recommended the disassembly of adrenaline autoinjectors after use, to access any remaining medicine. Disassembly of these devices can pose significant risks to patients and first aid providers, including needle stick injury, inappropriate administration and/or delay in accessing emergency medical care.

Adrenaline autoinjectors should be prescribed in accordance to relevant clinical guidelines, and should always be used in accordance to instructions in the Product Information.

The TGA has encouraged health-care professionals to advise patients to review the relevant Consumer Medicine Information leaflet.

Reference:
Medicines Safety Update, TGA, Vol. 7, No. 5, October-December 2016 (*www.tga.gov.au*)

Antidepressants

Communicating risks and benefits to patients

Australia. The TGA has issued a reminder to health-care professionals about the importance of communicating the potential risks and benefits of antidepressants, effectively to patients before prescribing them.

Concerns have been raised about an increase in the risk of suicidal thinking and behaviour when initiating antidepressants treatment, particularly selective serotonin reuptake inhibitors (SSRIs). Precautions relating to suicidal thinking and behaviour in children and adolescents are included in the Product Information documents of all SSRIs registered for use in Australia. These warnings are supported with information for patients included in Consumer Medicine Information documents for those products.

The TGA has encouraged health-care professionals to provide patients with the relevant Consumer Medicine Information for any new antidepressant they are prescribed.

Reference:
Medicines Safety Update, TGA, Vol. 7, No. 5, October-December 2016 (*www.tga.gov.au*)

Apremilast

Risk of suicidal thoughts and behaviour

The United Kingdom. The MHRA has stated that there is an increase in the risk of developing psychiatric symptoms such as depression, suicidal thoughts and behaviour with the use of apremilast (Otezla®). It is advised that treatment is stopped if patients have new psychiatric symptoms or if existing symptoms worsen.

Apremilast is used for the treatment of moderate to severe chronic plaque psoriasis or active psoriatic arthritis in adults who have not responded to other systemic treatments.

Clinical trials and postmarket experience have recorded serious psychiatric symptoms. Suicidal thoughts and behaviours have been reported in patients with no previous history of depression.

A review of the evidence from clinical trials and postmarket cases has suggested a causal association between apremilast and suicidal thoughts and behaviour. These events are reported to be uncommon, with an estimated frequency of between one in 1000 to 10 in 1000 patients taking apremilast.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 6:3, January 2017 *(www.gov.uk/mhra)*

Carbamazepine

HLA-B*1502 genotyping to minimize carbamazepine-induced severe cutaneous adverse reactions

Singapore. The HSA has reminded health-care professionals of the recommendation for HLA-B*1502 genotyping prior to the initiation of carbamazepine (CBZ; Tegretol® and generics) therapy in patients of Asian ancestry, to minimize risk of severe cutaneous adverse reactions (SCARs). This recommendation was stated in a joint Dear Health-care Professional Letter by the Ministry of Health and the HSA in April 2013.

CBZ is an anticonvulsant indicated for the treatment of epilepsy and other conditions such as bipolar disorders, alcohol-withdrawal syndrome,

trigeminal neuralgia, diabetic neuropathy and diabetes insipidus.

Between 2003 to 2012, the HSA received an average of 15 reports of CBZ-induced Stevens Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) per year. Since April 2013, more than 2,700 patients have been genotyped for HLA-B*1502, of which 11% were found to carry the HLA-B*1502 allele. The HSA has recently received one report of CBZ-induced SJS among all the patients screened for the allele. The suspected case of CBZ-induced SJS occurred in a patient who was genotyped negative.

While genotyping for HLA-B*1502 has successfully mitigated the risk of CBZ-induced SJS/TEN in Singapore, it has not been shown to be a risk predictor for CBZ-induced Drug Reaction with Eosinophilia and Systematic Syndrome (DRESS). The HSA has received two cases of DRESS in patients who were genotyped negative. These cases of CBZ-induced SCAR are a reminder of the need to remain vigilant for SCAR even among those who tested negative for HLA-B*1502, as non-genetic factors may be involved in the development of SCAR.

HLA-B*1502 genotyping test has proven highly effective in distinguishing high-risk patients from low-risk patients who can continue to use this cost-effective medicine.

Reference:
Product Safety Alerts, HSA, 20 December 2016 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.5, 2015: Risk of cerebrovascular adverse events in patients with vascular or mixed dementia in Australia)

Direct-acting antivirals to treat chronic hepatitis C

Interaction with vitamin K antagonists and changes in INR

The United Kingdom. The MHRA has informed health-care professionals of the potential fluctuation of international normalized ratio (INR) values in patients taking both vitamin K antagonists and direct-acting antivirals for chronic hepatitis C infection.

Vitamin K antagonists are used as anticoagulant medicines, and include warfarin and acenocoumarol.

A Europe-wide review of the use of concomitant vitamin K antagonists and direct-acting antivirals for chronic hepatitis C has identified that changes in INR occur during treatment. Changes in liver function secondary to hepatitis C treatment are thought to affect the efficacy of vitamin K antagonists.

The benefits of treatment with direct-acting antivirals for chronic hepatitis C continue to outweigh the risks of an interaction with vitamin K antagonists. However, INR values should be monitored closely in patients receiving this concomitant treatment because changes in liver function may affect INR values and necessitate adjustment of anticoagulant therapy.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 6:2, January 2017 *(www.gov.uk/mhra)*

(See WHO Pharmaceuticals Newsletter No.6, 2016: Interaction potential with warfarin and other vitamin K antagonists: changes to INR in Ireland)

Phenylephrine and acetaminophen

Drug-drug interaction, increased blood concentrations of phenylephrine: no significant risk to healthy consumers

Canada. Health Canada has helped raise awareness of a drug interaction between phenylephrine and acetaminophen among health-care professionals and consumers. Although the interaction may lead to an increased amount of phenylephrine in the body; to date there is no evidence to show that this is a significant risk to healthy consumers.

Phenylephrine and acetaminophen are drugs often found together in non-prescription health products used to relieve symptoms from the common cold, flu and allergies.

Health Canada initiated a safety review following a report by the EMA about the potential drug-drug interaction between phenylephrine and acetaminophen. People who have high blood pressure or heart disease may be more vulnerable to the adverse effects of phenylephrine if taken together with acetaminophen due to an increase in concentrations of phenylephrine in the body (increased bioavailability).

At the time of the review there was one Canadian report of increased blood pressure suspected to be due to a drug interaction between phenylephrine and acetaminophen. After further assessment, it was found that after adjusting pre-existing medication used for blood pressure the blood pressure returned to normal.

There is one published report in the scientific literature of intracerebral haemorrhage in a person taking multiple cough

and cold medicines containing phenylephrine over a 30-day period. It could not be confirmed that this event was due to an interaction between phenylephrine and acetaminophen. Overall, the safety data reviewed by Health Canada were lacking relevant information to determine if the drug-drug interaction between phenylephrine and acetaminophen causes adverse events.

Reference:
Summary Safety Review, Health Canada, 23 November 2016 (*www.hc-sc.gc.ca*)

Selective Serotonin Reuptake Inhibitors (SSRIs)

Potential risk of autism in children: not enough evidence

Canada. Health Canada has reviewed the risk of autism in children whose mothers used Selective Serotonin Reuptake Inhibitors (SSRIs) during pregnancy. The review was initiated following a publication in the scientific literature. Health Canada concluded that the available evidence is not strong enough to confirm that SSRI use during pregnancy can cause autism in exposed children.

SSRIs (citalopram (Celexa®), escitalopram (Cipralex®), fluoxetine (Prozac®), fluvoxamine (Luvox®), paroxetine (Paxil®) and sertraline (Zoloft®) and their generics) are prescription drugs to treat depression. Some are also authorized to treat anxiety disorders.

Health Canada reviewed 11 studies that investigated the potential link between SSRI use during pregnancy and the development of autism in exposed children. Some studies found a link while others did not. It was difficult to draw conclusions from these studies, as there was confounding by indication (it was difficult to separate the effects of mothers' mental illness from the effects of the medicine).

At the time of the review, Health Canada had received two Canadian reports of autism in children after SSRI use during pregnancy. Since the causes of autism are not well understood and there are many factors that may add to the overall risk, it was not possible to determine the role of SSRIs in the individual cases.

Reference:
Summary Safety Review, Health Canada, 6 January 2017 (*www.hc-sc.gc.ca*)

Sodium bicarbonate

Minimizing risk of intraventricular haemorrhage in pre-mature neonates

Egypt. The Egyptian Pharmaceutical Vigilance Center (EPVC) has made recommendations to minimize the risk of intraventricular haemorrhage in premature neonates during administration of sodium bicarbonate injection.

Sodium bicarbonate injection used in neonates is indicated for:

- correction of metabolic acidosis associated with cardiac arrest in patients with pre-existing metabolic acidosis;
- cardiac arrest associated with hyperkalaemia with pre-existing metabolic acidosis; and
- life threatening hyperkalaemia with pre-existing metabolic acidosis.

The recommendations are: 4.2% solution or 8.4% solution should be diluted with 5% dextrose 1:1; clinical need should be carefully considered before administration because rapid administration at a high concentration may be associated with fluctuation in cerebral blood flow and possibly intracranial haemorrhage.

The recommendations follow a report received at a regional centre in Egypt. A premature male neonate (26 weeks of gestation, 0.9 kg weight) received sodium bicarbonate 8.4 % to treat metabolic acidosis at a dose of dose 2mEq/kg and then developed intraventricular haemorrhage two days after drug administration. The patient died the following day.

Reference:
EPVC Newsletter, EPVC, Volume 8, Issue 1, January 2017

A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from individual case safety reports (ICSRs) available in VigiBase®, the WHO international database of suspected adverse drug reactions. The database contains over 14 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase® is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase® data is performed in accordance with UMC's current routine signal detection process.
More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 29). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. UMC's vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. For more information, visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: signals@who-umc.org.

Chymotrypsin and anaphylactic shock, a continuing safety issue

Dr Birgitta Grundmark, Uppsala Monitoring Centre and Prof Ambrose O Isah, Nigeria/Uppsala Monitoring Centre

During a UMC signal detection screening in September 2015, focused on reporting patterns in Latin America, Africa and Asia for both newly-marketed drugs and drugs which had been on the market for longer periods of time, the safety issue concerning anaphylactic shock in relation to single agent chymotrypsin was noted. While this serious adverse reaction from chymotrypsin is by no means a newly discovered one, a recent increase in reporting indicates a continuing safety issue worth addressing. It remains an issue in the parts of the world where the product is still on the market.

Introduction

Chymotrypsin is a digestive proteolytic pancreatic enzyme, present as one of several components of animal pancreas extracts indicated for the treatment of exocrine pancreatic insufficiency.

Apart from this essential usage, chymotrypsin as a single ingredient medicinal product has been and is still used in parts of the world for various indications outside the gastrointestinal tract.

In Europe and the USA, products containing solely chymotrypsin appear generally to have been withdrawn during the 1970-80s, according to the Swedish Medical Products Agency (MPA). Reasons for withdrawal are not always clear, but include commercial ones and the replacement of chymotrypsin with other, more modern products. Examples of its indications when in use in Europe, according to accessed approval documentation for products Kymo-Trypure, Chymar, Chymarex and Biozyme, provided by the MPA, were: to reduce trauma during cataract surgery, as an anti-inflammatory agent in relation to surgery or traumatic injuries, and as topical treatment of complicated wounds.

In parts of Africa and Asia, chymotrypsin is still available for topical and per-oral use as well as an injectable drug. Since regulatory approval differs internationally, and online labelling data is not readily available, a comprehensive assessment of the current use of chymotrypsin is difficult to make. However, information suggests that indications for use in countries where it is still on the market vary immensely, and include the following: as an anti-inflammatory agent, often in combination with antibiotics, for the resorption of inflammatory, postoperative and post-traumatic haematomas and oedemas, to dissolve in situ fibrinous inflammatory processes, in pelvic infections and inflammatory conditions including subsequent tubal sterility, in post-partum mammary engorgement, to dissolve airway secretions in chronic bronchitis and suppurative pneumonias, sinusitis, laryngitis and pharyngitis, in adhesive otitis, and syringitis, for arthritis, periarthritis, and Dupuytren's contracture, anthraxes, furuncles, abscesses, ulcers, eschars, and cheloid scars.[1]

Some Chinese sources mention its use in ophthalmic surgery, to reduce traumatic iridocyclitis, for local inflammation, secretion and oedema. Intravenous injection is discouraged due to the risk of serious side effects, and instead intramuscular injection is advised.

There appears to be some activity regarding clinical trials with chymotrypsin. Public databases list a Chinese study in an adult population on fallopian tube obstruction where

chymotrypsin is noted as part of the standard background treatment.[2] There is also a mention of a study on alimentary allergens in food products being treated with chymotrypsin to reduce allergenicity.[3]

The use of chymotrypsin as an anti-inflammatory agent has some scientific basis, including recent pre-clinical studies of its anti-inflammatory activity.[4] The use as a proteolytic enzyme to alleviate the symptoms of infections and effects of tubal occlusion also has some support in older sources.[5,6,7,8]

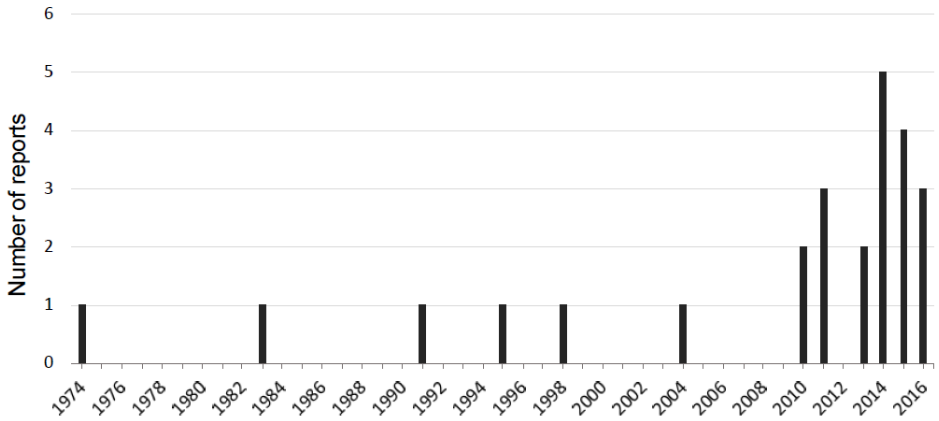
Anaphylactic shock is a severe and potentially fatal form of anaphylaxis, an allergic reaction. It can occur within seconds or minutes, up to hours, of exposure to the allergen. Signs and symptoms of anaphylaxis typically include more than one of the following: angioedema, urticaria, dyspnoea, wheezing, and hypoxemia, nausea, vomiting, abdominal pain, diarrhoea, light-headedness, dizziness, syncope, tachycardia, and in the most severe cases where the blood pressure is considerably affected, shock.

Websites presenting product information for chymotrypsin usually contain warnings and information on serious and severe allergic side effects; in most web sources anaphylactic shock is specifically mentioned.

The VigiBase® perspective

VigiBase®, the WHO international database of suspected adverse drug reactions, contains 25 cases of anaphylactic shock in relation to single-ingredient chymotrypsin treatment, which have been reported between 1974 and 2016 (Figure 1). 76% (19) of the cases have been submitted since 2010, almost exclusively from a few member states in Asia and Africa as they have entered the WHO Programme for International Drug Monitoring and subsequently started actively submitting their cases to VigiBase®. The 25 reports originate from China (9 cases), Thailand (1), Vietnam (7), Egypt (3), France (3), Romania (1) and Germany (1). A further 11 cases reported were for multi-enzyme extracts used to treat exocrine pancreatic insufficiency but these are not discussed further here. To put these figures into context, as of 1 September 2016, the total number of ICSRs submitted for chymotrypsin for any ADR in VigiBase® is 317. 71% of these have been submitted since 2010, almost exclusively from Asia and Africa.

Figure 1. Timeline of submission by the National Centres into VigiBase® of case reports of anaphylactic shock in relation to chymotrypsin



Reports in VigiBase®

In the 25 reports, the median age of the patients is 36 years with a range of 1-71 years. Most of the reports, 76%, concern women. Indication for treatment in the 10 cases where this is stated are: acute salpingo-oophoritis (1 case), haemorrhoids (1), post-operative anti- inflammatory treatment for oedema (2), inflammation n o s (1), superficial injury of head (1), superficial injury of trunk (1), acute pharyngitis (1), and prophylactic chemotherapy (2, where the chemotherapy appears to refer to co-prescribed antibiotics). An antibiotic is co-prescribed in many of the cases. The dosage form, where this is noted, is intramuscular injection (9 cases), intravenous injection (2), subcutaneous injection (1), topical (1) and oral administration (1). In a majority of the reports (20 cases) chymotrypsin is the only suspected drug. There appears to be a fatal outcome in one of the cases although a narrative for this, the very first one, reported from the Federal Republic of Germany in 1974, is lacking. In a few cases a co-suspect drug, usually an antibiotic, was administered, but since anaphylactic shock is indeed an acknowledged risk of chymotrypsin the causality is not discussed further for the reported cases.

Conclusion

While chymotrypsin as a single ingredient medicinal product has been replaced with other drugs with more positive risk-benefit profiles on the European and US markets, the substance appears still to be extensively used elsewhere, and thus not only in the countries from where the latest case reports in the detected case series originate, one example being Nigeria. Considering the ever-present under-reporting and the apparent widespread use, including in some resource-limited settings with less well-established ADR reporting systems, it is likely that unreported cases of anaphylactic shock are occurring in such countries in addition to the ones which have already reported cases into VigiBase®. Hence, potentially fatal anaphylactic shocks in relation to chymotrypsin use may be appearing where the facilities for successful treatment of it may be lacking, making it particularly dangerous. We believe that in light of this reaction, continuing use of chymotrypsin is of concern in resource-limited settings and should be re-evaluated in countries where it is still available, taking into consideration the respective national pharmacotherapeutic and clinical access situation and tradition.

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Ganciclovir and hypoglycaemia

Dr Richard Day, Australia

Summary

Twenty-one individual case safety reports of hypoglycaemia in association with ganciclovir have been submitted to VigiBase®, the WHO international database of suspected adverse drug reactions, up to 3 December 2015. The association has an IC value of 0.22 and an IC_{025} value of -0.46. The reports originate from the United States, Japan, United Kingdom, Australia, Israel and the Netherlands. These cases have occurred in immunocompromised patients, some of whom have HIV or malignant blood disorders prior to exposure to ganciclovir. Usually the drug was given intravenously, the indication presumably for suspected or actual cytomegalovirus (CMV) infection. A number of the cases reported concomitant anti-hyperglycaemics for diabetes and, occasionally, antibiotics known to rarely cause hypoglycaemia. The possibility of drug interactions is noted, for example with sulphamethoxazole/trimethoprim. In addition, many of these patients were very unwell. In the literature a striking case describing repeated hypoglycaemic episodes with repeated recommencement of ganciclovir, and in two cases in the VigiBase® case series, re-challenge with ganciclovir caused hypoglycaemia. Also, the time to onset of hypoglycaemia was relatively short. From these reports, the risk of hypoglycaemia associated with ganciclovir is very uncertain but the occurrence of hypoglycaemia resolving on cessation and recurring upon re-exposure in some cases demands consideration.

Introduction

Ganciclovir is an acyclic nucleoside analogue used to treat and prevent cytomegalovirus (CMV) infections after solid organ transplantation (SOTR), and in immunocompromised patients such as those with HIV. CMV is a herpes virus that causes very serious disease in these patients. In SOTR, CMV infection is the most frequent complication and leads to a significant increase in mortality.[1] Ganciclovir has been shown to have good efficacy in preventing and treating CMV infections.[2] The main toxicity is dose-related leukopenia, and therapeutic drug monitoring is used increasingly to reduce the risk of this complication.[3] The drug is administered intravenously to treat CMV and orally to prevent this infection.[4,5] Valganciclovir, a pro-drug for ganciclovir, has been introduced because of its superior oral bioavailability and the prospect of more effective prophylactic treatment and less need to use the intravenous route. The ganciclovir label does not have a warning for hypoglycaemia.[6]

Hypoglycaemia indicates that blood glucose concentrations have fallen to such an extent that physiological functions dependent upon a supply of glucose are affected, most notably brain function. Dizziness and loss of consciousness, along with evidence of autonomic nervous system activation including sweating and tachycardia, occur. There is considerable hazard associated not only from injury but also, in the case of repeated episodes, brain damage.

Reports in VigiBase®

In VigiBase®, the WHO international database of suspected adverse drug reactions, there have been 21 cases associating ganciclovir and hypoglycaemia, submitted between July 1989 and August 2015 (presented in Table 1). The association has an IC value of 0.22 and an IC025 value of -0.46. Of the reports, four were female, two of unknown sex and 15 were male. Their ages ranged from 10 to 84 years but most were in their 30s or 40s (median 40 years). The reports originated from the United States (12), Japan (4), United Kingdom (2), Australia (1), Israel (1) and the Netherlands (1). Five were designated as serious, one not serious, and the remainder not classified. In one 37-year-old male, the effect was considered 'life-threatening' and in a 44-year-old male, 'life-threatening, prolonging hospitalisation'; this patient died. Time to onset ranged from 0 to 273 days with a median of six days.

Ganciclovir was administered intravenously in all but one patient who was given it orally and another where it was not recorded. It is presumed that the indication for the drug was CMV treatment or prophylaxis as these were listed for only three patients - CMV chorioretinitis, opportunistic infection, and a third case was listed as chorioretinitis and retinochorioditis. These three cases were not in HIV patients as inferred from co-medications recorded. In the 21 patient group there appeared to be four HIV patients.

Relevant co-morbidities in these patients can be inferred in some cases by concomitant medications. In particular, drug treatments for diabetes are very relevant. There were four patients with diabetes and three of these were taking insulin therapy. One patient was taking glimepiride and metformin, both reported as suspected along with ganciclovir. Glimepiride is a sulfonylurea anti-hyperglycaemic drug used in type II diabetes mellitus and hypoglycaemia is a well-established adverse drug reaction. This is more likely in the elderly and renally and/or hepatically impaired. The patient in question was aged 65 and female but her plasma creatinine concentrations were low/normal and liver function tests were normal. Other medicines included loxaprofen, an NSAID, that may have reduced her renal function, but as noted, renal function appeared normal. The dose of glimepiride was 3 mg twice daily which is in fact a large dose, raising the strong possibility that this drug was related to the hypoglycaemia. The metformin she was taking was also ceased at the same time as the glimepiride but it is not associated with hypoglycaemia. It appears that this patient had been on glimepiride and metformin before the ganciclovir was commenced, the indication being for CMV chorioretinitis. The hypoglycaemic event occurred after 10 days exposure to ganciclovir, the dose being 250 mg twice daily iv. In this case, a re-challenge of ganciclovir with a recurring reaction is reported. There is no report of re-challenge of the co-suspected medication, suggesting that for the re-challenge, ganciclovir was the single cause.

A 67-year-old male was also taking insulin daily. Another two patients, a 40-year-old male on ganciclovir 300 mg/day iv and a 35-year-old male prescribed ganciclovir 700 mg/day iv were also taking insulin. Two of the patients taking insulin had a fairly long time to onset from ganciclovir treatment start (77 and 62 days respectively). It is reasonable to infer that all were taking the anti-hyperglycaemic medicines prior to commencing ganciclovir. CMV infection has a weak association with diabetes and cardiovascular disease,[7] but none of the 21 other patients had anti-hyperglycaemic drugs listed as co-medications. Further, the accounts of diabetes in association with CMV do not record hypoglycaemia as a particular feature, although this can occur in patients with diabetes mellitus, as is well known.

Table 1. Characteristics of case reports in VigiBase® of hypoglycaemia in association with ganciclovir

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Dose	Reactions (WHO-ART preferred terms)	Time to onset	Dechallenge/Rechallenge	Outcome
1	67/F	Sulfamethoxazole/trimethoprim (S) Prednisolone (C)	2.5 mg/kg, 1 per1day	Hypoglycaemia	1 day	No dechallenge/ No rechallenge	Unknown
2	82/M	-	-	Hypoglycaemia, blood sugar decreased	-	Unknown dechallenge, reaction abated	Recovered
3	84/M	-	-	Blood sugar decreased	-	Unknown	Unknown
4	65/F	Glimepiride, metformin (both S) Brotizolam, loxoprofen, magnesium oxide, oxycodone, rebamipide (all C)	250 mg, 2 per 1 day	Hypoglycaemia	10 days	Positive dechallenge/ Positive rechallenge	Recovered
5	37/M	Ceftriaxone (S) Amphotericin b, esomeprazole, lactulose, liquid food*, potassium chloride iv*, calcium gluconate iv* (all C)	1000 mg, 1 per 24 hours	Hypoglycaemia	1 day	Positive dechallenge	Recovering
6	44/M	Atazanavir, ciprofloxacin, didanosine (all S) Abacavir, amphotericin b, azithromycin, dapsone, enfuvirtide, erythropoietin human, ethambutol, gabapentin, iron, lamivudine, morphine, stavudine, tenofovir (all C)	350 mg, 1 per 1 day	Respiratory distress syndrome, ALT increased, AST increased, bilirubinaemia, hypoproteinaemia, hypokalaemia, hyponatraemia, azotaemia, coma, hypoglycaemia, hypotension, pancytopenia, pneumonitis, respiratory, insufficiency, sepsis, vomiting	167 days	Unknown	Died
7	55/F	-	340 mg, - per 1 day	Hypoglycaemia	6 days	Unknown	Recovered
8	10/M	Colistin, methylprednisolone, neomycin, teicoplanin, tranexamic acid (all C)	300 mg, - per 1 day	Hypoglycaemia	5 days	Unknown	Recovered
9	-/M	-	-	Hypoglycaemia	0 days	Dose not changed	Unknown
10	67/M	Fluconazole, insulin, sulfamethoxazole/ trimethoprim, tacrolimus (all C)	-	Hypoglycaemia, coma	77 days	Unknown	Unknown
11	38/M	Atenolol, metronidazole, sodium bicarbonate, sulfamethoxazole/trimethoprim (all C)	-	Hypoglycaemia, tremor	-	Unknown	Unknown
12	-/-	Sulfamethoxazole/trimethoprim (C)	-	Hypoglycaemia	-	Unknown	Unknown
13	-/-	-	-	Hypoglycaemia, nervousness, dizziness	-	Positive rechallenge	Unknown
14	40/M	Insulin, pyridoxine hydrochloride/tyrosine/ nicotinamide (both C)	300 mg, - per 1 day	Hypoglycaemia	62 days	Unknown	Unknown
15	31/M	Didanosine, erythropoietin human, fluconazole, pentamidine (all C)	400 µg** - per 1 day	Hypoglycaemia	273 days	Unknown	Unknown
16	34/M	Pyridoxine hydrochloride/tyrosine/ nicotinamide (C)	-	Hypoglycaemia	-	Unknown	Unknown
17	29/M	Amitriptyline, cycloserine, hydroxyzine, pethidine (all C)	600 mg, - per 1 day	Hypoglycaemia	6 days	Positive dechallenge	Unknown
18	35/M	Aciclovir, ibuprofen, insulin (all C)	700 mg, - per 1 day	Hypoglycaemia, tremor, confusion, fatigue	3 days	Unknown	Unknown
19	33/M	Gentamicin, ketoconazole, mezlocillin, paracetamol (all C)	-	Hypoglycaemia	-	Unknown	Recovered
20	39/F	Ketoconazole, methadone, sulfamethoxazole/trimethoprim, zidovudine (all C)	600 mg, - per 1 day	Hypoglycaemia, death	11 days	Unknown	Died
21	41/M	Aciclovir, amoxicillin, atropine sulfate/ diphenoxylate hydrochloride (all C)	-	Hypoglycaemia	1 day	Unknown	Recovered

** Reported drug*
*** Suspected reported error*

Five patients were concomitantly taking sulfamethoxazole/trimethoprim, presumably as prophylaxis against pneumocystis carinii pneumonia (PCP) and toxoplasmosis in immunocompromised individuals. However, the drug is rarely associated with hypoglycaemic attacks, these more commonly occur in patients with renal impairment given large doses.[8] Unfortunately, our reports do not include the doses of sulfamethoxazole/trimethoprim or renal function in these patients.

Case 5 was on ceftriaxone for three days and the hypoglycaemic event occurred on day 3 when this drug was ceased. Ganciclovir in a large dose had been commenced on day 2 of the ceftriaxone treatment.

Both were stopped on day 3 when the reaction was observed, so, the reaction occurred only after the ganciclovir was commenced and resolved on cessation of these drugs. These cases of concomitant antibiotics and ganciclovir may represent a drug interaction. However, a mechanism is not obvious.

The doses of ganciclovir varied significantly from 2.5 mg/kg iv daily, to 1000 mg iv daily, the wide range reflecting prophylactic to treatment doses. Nine of our 21 reports (of which 14 reported a time to onset) occurred within 10 days of commencing ganciclovir and five within three days. Of these, one was linked by the reporter to ibuprofen, that is highly unlikely, and the other to ceftriaxone, again quite unlikely.

Case 13 is recorded as having been re-challenged and experiencing hypoglycaemia, along with nervousness and dizziness. However, there is very little detail in this report raising some uncertainty whether these symptoms recurred upon re-challenge.

Discussion and Conclusion

There are sparse reports of ganciclovir possibly causing hypoglycaemia in the literature.[9,10] A striking case occurred with repeated treatments with ganciclovir in an infant with CMV associated cholestasis. Repeated hypoglycaemic episodes with repeated recommencement of ganciclovir in this patient makes a causal connection hard to dispute.

There is no obvious mechanistic reason for this possible adverse reaction. However, in a number of these reports, the time to onset of hypoglycaemia was relatively short after exposure to ganciclovir. Additionally, in two cases re-challenge with ganciclovir caused hypoglycaemia and even though one of these cases is not very informative, the other seems to have withdrawn three suspected drugs and re-initiated only ganciclovir, after which the reaction recurred. Thus, the most convincing data of an association emerging from these cases is the short time to onset and recurrence on re-exposure, the latter a strong indication of causality. For these reasons this association is worthy of attention and further investigation.

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Lamivudine and hearing decreased

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Summary

Lamivudine is a nucleoside reverse transcriptase inhibitor indicated for the treatment of HIV/AIDS as a component of the multi-drug highly active antiretroviral therapy (HAART) regimen, and also for the treatment of hepatitis B. The WHO international database of suspected adverse drug reactions, VigiBase®, holds 45 reports of lamivudine and hearing decreased which is not labelled as an adverse drug reaction. The individual case safety reports (ICSRs) are from 13 countries across all continents. After exclusion of poor quality reports, 19 of the ICSRs were evaluated in depth. In these, lamivudine was mostly co-prescribed with other ARTs, notably stavudine, zidovudine, ritonavir, and nevirapine. The time to onset ranged from 4 days to 5 years (median 9 months) with the main cluster at 2 to 10 months.

The country-spread buttressed the strength and consistency of the association. The biological plausibility, coherence and temporality of the association is evident from the mitochondrial toxicity of lamivudine and the exposure to event time observed. The smaller number of reports from patients being treated for hepatitis B on a lower dose of lamivudine may suggest a biological gradient. The importance of the experimental findings of the effect of lamivudine in vitro on a cochlear cell model further supports the association; coupled with the occurrence of hearing impairment in a medical student following the use of lamivudine, stavudine, and nevirapine for post-exposure prophylaxis.

Despite the inability to fully dissociate the effects of the co-administered ARTs, against a background of the confounding effects of the primary disease, the evidence is suggestive of a possible causal effect relationship of the lamivudine-hearing decreased combination.

Introduction

The drug-event combination of lamivudine and hearing decreased was prioritised for further clinical review in a signal detection screening of VigiBase®, the WHO international database of suspected adverse drug reactions, in September 2015. The screening focused on drug-event combinations sensitive to reporting patterns in mainly Africa, Asia, and Latin America and the Caribbean.

Lamivudine is a nucleoside reverse transcriptase inhibitor (a cytidine analogue), first manufactured in 1988, and approved for use in 1995 by the U.S. Food and Drug Administration (FDA). Its introduction into the therapeutic management of HIV/AIDS coincided with the introduction of the Highly Active Antiretroviral Therapy (HAART) regimen which ended the era of zidovudine monotherapy.[1-3] The lamivudine/zidovudine combination was approved soon after by the FDA in 1997. Lamivudine is used in combination therapy as backbone with other Nucleoside or Nucleotide Reverse Transcriptase Inhibitors (NRTI or NtRTI), with medicines of other classes notably the Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) and Protease Inhibitors (PI). The essential mechanism of action of lamivudine is by conversion intracellularly into its triphosphate form which competes with cytosine triphosphate for incorporation into the developing viral DNA strand. Consequently, the developing DNA chain terminates and arrests the development of the viral DNA. Toxicity of lamivudine results from mitochondrial dysfunction as it reduces mitochondrial DNA (mDNA) levels in various tissues, including the cochlear, via polymerase gamma (γ) – inhibition.[4,5] The other use of lamivudine is in the treatment of chronic hepatitis B.[6] However, the dosage regimen used in this instance is lower than that for the treatment of HIV/AIDS. Of interest is a case control study from Oman, which showed a significant hearing loss in 95 patients with hepatitis B infection.[7]

Decreased hearing could be a peculiar drug-induced reaction, the occurrence of which could ultimately result in defective communication. The observation of this reaction in HIV/AIDS patients followed the success of therapy which prolonged the life of these patients. It became necessary to address the quality of life of patients who hitherto had succumbed to their disease. Since its recognition, studies have shown that a substantial proportion of patients (27.5 - 33.5%) with HIV/AIDS do suffer from hearing loss in the course of the disease.[8,9] There remains the ongoing debate as to the burden of hearing impairment in antiretroviral therapy (ART)-naïve patients.[10]

The potential for a drug-induced hearing loss in an HIV-infected individual at any stage of the disease was reported to be relatively high.[11] Smidon et al. was early to highlight this possibility in three case reports following ARTs. He noted confounding factors in the interpretation of the findings notably prior hearing loss from other causes including infections, history of noise exposure and older patients (≥35years).[12] Conclusions could not be reached from these early observations.

Cohen et al. characterised hearing loss associated with HIV infection as having any of the following attributes: unilateral or bilateral,

progressive or sudden in onset, conductive or sensorineural or mixed.[9]

Reports in VigiBase®

As of June 2016 VigiBase® contained 45 ICSRs, after exclusion of six suspected duplicate reports, with lamivudine and the WHO-ART High Level Term (HLT) hearing decreased, entered over a period of almost 19 years (May 1997 to April 2016). Of these, 26 reported the preferred term (PT) hearing decreased, 19 deafness, and 1 deafness nerve (one case reported both hearing decreased and deafness and is hereafter counted only in the deafness category). The PT hearing decreased included at the Included Term (IT) level the following terms: auditory hypoacuity (1 case); hearing decreased (15); hearing impaired (7); and hypoacusis (2), while the PT deafness included at the IT level the following terms: deafness (14 cases); deafness unilateral (2); and hearing loss sudden (3).

There were nine 'serious' cases and one death co-reported with hearing decreased (PT) and another nine for deafness (PT) with no reported deaths. The reports included 12 males and 13 females aged 0-62 years (hearing decreased); 16 males and 3 females aged 0-60 years (deafness); and one male aged 42 years (deafness nerve).

The ICSRs were from 13 countries in five continents, showing a fairly global distribution: Africa (Nigeria, South Africa); Asia (South Korea, Japan); Europe (Belgium, Germany, France, Spain and Switzerland); North America (Canada, USA); Latin America (Peru) and Oceania (Australia).

The documentation grading of the ICSRs, as determined by the vigiGrade™ completeness score, ranged from 0.18-1.0.

Nineteen reports contained sufficient information for more in depth assessment and these are shown in Table 1. The remaining 26 ICSRs (18 mentioning hearing decreased, 7 deafness, and the case with deafness nerve reported) had incomplete relevant fields, especially dates of drug administration and event onset.

A feature for nearly all the 19 cases was the use of the HAART regimen with multiple ART medicines. There were mainly co-prescriptions with stavudine (7 cases), zidovudine (6), ritonavir (5), and nevirapine (4). The additional medicines co-prescribed with lamivudine were as recommended for the standard HAART regimen for the treatment of HIV/AIDS. In six cases sulphamethoxazole/ trimethoprim was co-prescribed. Two cases reported medicines with high ototoxic potential: anti-tuberculosis treatment (case 8) and amphotericin b (case 7) for fungal infection.

The outcomes of the cases were as follows: recovered (1 case), recovering or recovered with sequelae (8), not recovered (3) and unknown (7). Unfortunately, dechallenge information was unclear in most of the reports of recovery or partial recovery. However, one report (case 19) mentioned a positive dechallenge.

Three case reports are of interest because HIV/ AIDS was unlikely to be the cause of hearing loss. In one (case 12) HAART was given for post-exposure prophylaxis. Onset of the deafness was two to three weeks after the medicines were discontinued and the patient subsequently was recovering. The other two patients were given lamivudine monotherapy for chronic hepatitis at a lower dose of 100 mg daily (cases 1 and 5). It is of interest that one of these patients (case 1) was also on an herbal medicine with possible otoprotective effect, *Silybum marianum*, and had a time to onset of 5 years.[13] The time to onset of the event for all the cases ranged from 4 days to 5 years (median 9 months). The other patient treated for hepatitis continued lamivudine and had not recovered at the time of reporting.

Literature and Labelling

The product labels for lamivudine, approved by various regulatory agencies, including EMA, FDA and Health Canada, do not list decreased hearing as an adverse drug reaction.[14-16] Martindale also does not give this as an adverse drug reaction.[17]

Hearing dysfunction was one of the clinical manifestations realised as soon as the various subspecialties in medicine appreciated the manifold presentation of HIV/AIDS, with the prevalence of hearing defects put at 27.5 - 33.5% in the late 1980s to early 1990s, and sudden hearing loss reported by Real et al. in 1987.[8,9,18] The disparity in prevalence is heightened by the disclosure of 2% in an Indian series.[19] Though these early clinical presentations appeared to precede the effective introduction of the ARTs, in 1998 Kohan et al. highlighted ototoxic medications as a possible cause.[20]

The introduction of the HAART regimen, soon after the approval of lamivudine, implied that lamivudine was used from the beginning in combination therapy, not allowing for the identification of any peculiar adverse effects.[2,3] The overall dramatic life-threatening nature of HIV/AIDS also meant that the health of non-vital sensory organs was given minimal consideration.

In one of the early studies on hearing loss following the introduction of the ARTs, Marra et al. conducted a case control study which showed that 29% of patients had hearing loss, this being most pronounced in patients on ARTs.[8] Identified risk and confounding factors included age (>35 years) and infections. In 1997, Monte et al. reported the sudden onset of hearing loss in a 31-year-old African woman diagnosed HIV positive occurring 10 days after

being placed on zalcitabine, an NRTI. Despite stopping the drug the hearing loss persisted.[21]

In another remarkable case-report, Rey et al. highlighted a case from France of a 23-year-old female medical student who was administered ART combination of stavudine-lamivudine-nevirapine for post-exposure prophylaxis. She was prescribed nevirapine for four days and the other two for one month. Less than two weeks after the end of NRTI treatment she developed sudden bilateral hearing loss, with partial recovery after several months. No abnormality was found despite an in-depth investigation. She remained HIV negative after six months.[22] It is likely that this patient is case 12 of the VigiBase® case series in Table 1.

Table 1. Characteristics of case reports in VigiBase® of decreased hearing in association with lamivudine

Case	Age/Sex	Suspected (S) or concomitant (C) drugs	Reactions (WHO-ART preferred terms)	Time to onset	Outcome	Comments
1	62/M	Lamivudine (S) Silybum marianum (C)	Hearing decreased, asthenia, fatigue, torticollis, dizziness, abdominal pain, ear disorder nos	5 years	Recovered	Treatment for chronic hepatitis
2	9/F	Lamivudine, ritonavir/lopinavir, abacavir (all S)	Hearing decreased	2 months	Unknown	
3	25/F	Lamivudine (S) Stavudine, nevirapine, sulphamethoxazole/ trimethoprim (all C)	Hearing decreased	7 months	Unknown	
4	27/F	Lamivudine (S) Zidovudine, nevirapine, sulphamethoxazole/ trimethoprim (all C)	Hearing decreased	3 years	Unknown	
5	38/F	Lamivudine (S)	Hearing decreased, tinnitus	9 months	Not Recovered	Treatment for chronic hepatitis
6	57/M	Lamivudine, levodopa/benserazide hydrochloride, ritonavir, tenofovir, tipranavir, sulphamethaxazole/trimethoprim (all S)	Hearing decreased, tinnitus	10 months	Recovering	
7	41/M	Lamivudine, stavudine, amphotericin b (Fungizone), amphotericin b (Amphotericin b liposome) (all S)	Hearing decreased, deafness	4 years	Recovering	Antifungal therapy
8	43/M	Lamivudine, pyrazinamide, zidovudine, isoniazid, indinavir, ethambutol (all S)	Hearing decreased	1 month	Not Recovered	Anti-tuberculosis therapy
9	40/F	Lamivudine, tenofovir (both S) Sulphamethoxazole/trimethoprim (C)	Tinnitus, paraesthesia, deafness, arthralgia	5 months	Recovering	
10	35/M	Lamivudine, tenofovir, nevirapine (all S)	Deafness	4 years	Unknown	
11	39/M	Lamivudine ritonavir, abacavir, fosamprenavir (all S)	Deafness	14 months	Recovering	
12	24/F	Lamivudine, nevirapine, stavudine (all S)	Deafness	2 months (2-3 weeks after withdrawal)	Recovering	Post-exposure prophylaxis
13	39/M	Lamivudine, nelfinavir, abacavir (all S)	Deafness	3 months	Recovering	
14	49/M	Lamivudine, stavudine, zidovudine (all S) Sulphamethoxazole, trimethoprim, efavirenz (all C)	Tinnitus, ototoxicity, deafness, condition aggravated	3-15 months*	Unknown	
15	51/M	Lamivudine, abacavir, stavudine, zidovudine, didanosine (all S) 10 nonspecified drugs (unknown S or C)	Deafness, vitamin B12 deficiency, tinnitus, ototoxicity, neuropathy peripheral, condition aggravated	1-24 months*	Recovered with sequelae	Reactions started before introduction of abacavir, zidovudine and didanosine
16	47/M	Lamivudine, didanosine, stavudine, hydroxycarbamide, efavirenz (all S)	Ototoxicity, deafness	1-24 months*	Unknown	Reactions started before introduction of didanosine, hydroxycarbamide and efavirenz
17	35/M	Lamivudine, zidovudine, indinavir, fluconazole, sulphamethoxazole/trimethoprim (all S)	Deafness, fatigue, headache, blindness, vision abnormal, anaemia	10 months	Not recovered	
18	53/M	Lamivudine, ritonavir, zidovudine (all S)	Cranial nerve disorder, deafness	2 months	Unknown	
19	47/M	Lamivudine, stavudine, ritonavir, (all S)	Deafness, ear disorder nos	4 days	Recovered with sequelae	Positive dechallenge

**Unclear time to onset because nonspecific dates of drug administration and/or event onset were provided (YYYY-01-01).*

In 2001, Smidon et al. reported three cases of possible ototoxicity from NRTIs.[12] In one of the cases the audiology record of a patient on zidovudine monotherapy (pre-HAART era) revealed a decline in hearing over a nine-year period from near upper limits of normal to severe bilateral deafness. There were no associated opportunistic infections though he had suffered from noise exposure a decade earlier. In another case in this series, a 49-year-old veteran initiated with efavirenz, stavudine, lamivudine and sulphamethoxazole/trimethoprim developed symptoms about four months after commencement which worsened over a two-month period. On discontinuation of stavudine and start of zidovudine, there was partial resolution of symptoms after one month. It was postulated that myriad factors, including ageing, infection and hearing loss, were associated with mitochondrial DNA mutations, and since NRTIs cause mitochondria toxicity, synergy with mitochondrial abnormalities induced by these factors may produce enhanced auditory dysfunction as has been earlier reported.[23]

Schouten et al. performed a longitudinal, prospective study of the hearing changes following zidovudine and didanosine therapy, both NRTIs, over a 32-week period. This study measured changes in hearing levels at all frequencies and also in low- and high-frequency, pure tone averages. No significant changes were observed. Lamivudine was not evaluated in this study.[24]

In a very elaborate in vitro study, 14 antiretroviral drugs across the various classes of NRTI, NtRTI, NNRTI and PI, as well as combinations of these drugs were investigated using the HEI-OC1 auditory cells (cell viability, flow cytometry, and caspases 3/7-activation). While all the ARTs showed some degree of cytotoxicity, the high degree of toxicity shown by some lamivudine-containing combinations, abacavir/lamivudine (Epzicom®), abacavir/lamivudine/zidovudine (Trizivir®) among others, was of particular interest.[25] However, using other cell lines such as the human hepatoma cells, Venhoff et al. reported minimal toxicity of tenofovir and lamivudine, a moderate effect for emtricitabine and a strongly impaired proliferation of cells with abacavir and zidovudine. The authors noted that the interaction amongst the NRTIs appeared to be unpredictable.[26] In another earlier study, Kakuda highlighted the hierarchy of mitochondrial DNA polymerase gamma inhibition: zalcitabine > didanosine > stavudine > lamivudine > zidovudine > abacavir.[27] From the above in vitro studies, it is possible that lamivudine alone or in combination with other ARTs may exert toxic effects by its action on the mitochondria of cochlear cells – a known pathway for ototoxicity.

Discussion

Human interaction and communication is facilitated by the sense of hearing. The lamivudine - hearing decreased combination poses a dilemma in the face of the standard of care which requires the use of a minimum of a triple regimen. The actions - beneficial and adverse - are inextricably linked since they act by the same mechanism. However, many health professionals realise that there may be a complex interplay of factors, including but not limited to a direct action of the virus causing the primary disease, opportunistic and other infections, (accelerated) ageing, environmental noise, past injuries with the ototoxic effect of medicines used in the treatment of HIV/AIDS and opportunistic infections (aminoglycosides for tuberculosis, amphotericin b for fungal infections). The impact of any given factor may be more profound depending on prevailing circumstances where they may chronically impair hearing or abruptly disrupt the process. Despite the difficulties of identifying and isolating these confounders, numerous findings suggest an effect by the ARTs, notably lamivudine, on auditory function.

Using the Bradford Hill criteria, the consistency observed by the reports across the 13 countries underscores the importance of this combination.[28] The number of cases assessed in-depth are limited by the quality of the ICSRs, with a number of reports excluded from further assessment due to the absence of important data such as the start and end dates of medication, time to onset of event, outcomes etc. The number may also be limited by low reporting from countries especially in Africa where the volume of ART use is high but the pharmacovigilance systems rudimentary.

In this case series lamivudine was suspected to cause auditory dysfunction with varying levels of severity. As mentioned above the suggested mechanism of action is by the drug-induced mitochondrial DNA reduction, which gives credence to a biological plausibility, further supported by the link with ageing found in the primary disease state.[23] The series may also suggest some biological gradient through the observation of limited cases from patients treated for chronic hepatitis with a much lower dose than those for HIV/AIDS. The experimental findings from the in vitro models highlighted the effects of lamivudine and other ARTs on cell assays. Again the outcome following dechallenge in one case is also suggestive of an association. Of interest is the finding of the enhanced effect of lamivudine containing combinations. This is also found in the database where ICSRs of lamivudine - hearing decreased exceeds those of other ARTs, although this observation must be interpreted with caution due to lack of denominator data. Furthermore, a 32-week longitudinal study with zidovudine/didanosine, using a battery of auditory tests, did not show significant changes in hearing. An interesting observation is the temporality with a time to onset ranging from 4 days to 5 years (median

9 months). The herbal medicine *Silybum marianum* used by the patient with the longest time to onset of 5 years has been shown in animal studies to protect against noise induced hearing loss.[13]

The occurrence of the event seems to occur against a background of the disease process. The other factors at play might include the genetic susceptibility of the patient, concomitant infections and the interaction with other medicines including the HAART drugs. The sudden onset found in some instances might support this, as in the case of the HIV negative medical student administered post-exposure prophylaxis.[22] Incidence of hearing loss doubles in HIV positive patients with tuberculosis treated with ARTs. In this series there were three cases treated with anti-tuberculosis drugs. An analogy could also be inferred from the aminoglycoside-induced ototoxicity which involves the cochlear neuroepithelium leading to sensorineural hearing loss. The action on the mitochondria in the genetically pre-disposed patients can also be profound.[29]

The co-prescription of lamivudine with other NRTIs or NtRTIs might suggest the possibility of some interaction predisposing patients to high toxic levels. However, this class of medicines is not metabolised by the cytochrome P450 enzyme system and lamivudine is mainly (70%) eliminated by the kidneys.[30] No significant pharmacokinetic interaction is known to occur with zidovudine or abacavir.[31] It is also unlikely to interact with the protease inhibitors including lopinavir/ritonavir used predominantly in this series.[32] However an increase in the AUC and decreased renal clearance was observed when co-administered with trimethoprim, while the inverse does not occur.[30] A number of HIV/AIDS patients are co-administered co-trimoxazole, as was the case in this series.

The low reporting rate from countries where there is a high burden of HIV/AIDS might be due to the rudimentary pharmacovigilance systems and the low index of suspicion of this event which has not been accorded due priority for the disease.

Conclusion

The evidence from VigiBase® and the fulfilment of most of the Bradford Hill criteria suggests an association between lamivudine and decreased hearing. The reports from 13 countries gives credence to the strength of the association and consistency. The biological plausibility, coherence and temporality of the association is evident from the mitochondrial toxicity of lamivudine and the exposure to event time observed. The fewer reports from patients being treated for chronic hepatitis, with a lower dose of lamivudine, may suggest a biological gradient. Other experimental findings - in vitro and clinical - and the analogy drawn from ototoxicity of anti-tuberculosis medicines further strengthen the evidence. Limitations are a lack of specificity as in most cases lamivudine was given in a HAART combination, although the lack of a consistent pattern of combinations in the reports suggests a role for lamivudine, and unclear documentation of dechallenge in most patients.

Occurrence of decreased hearing in lamivudine monotherapy for chronic hepatitis in two cases lends further support of the association, while co-administration with other ART medicines in the majority of the cases might suggest a class effect or possibly potentiation. It would neither be ethical to use the medicines (NRTIs) as monotherapy in the treatment of retroviral disease to further confirm this effect, nor would it be prudent not to highlight this possible association. In effect, while the underlying primary disease in HIV/AIDS patients remains a possible cause, the role of the ART medicines should be given due consideration especially in susceptible patients.

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CAVEAT DOCUMENT

Accompanying statement to data released from VigiBase®, the WHO international database of suspected adverse drug reactions

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring (PIDM). The information is stored in VigiBase®, the WHO international database of suspected adverse drug reactions (ADRs). It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.
Some National Centres that contribute information to VigiBase® make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

If in doubt or in need of help for interpretation of country specific data, UMC recommends to contact the concerned NC before using the data.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Confidential data
According to WHO policy and UMC Guidelines, ADR reports sent from the WHO PIDM member countries to VigiBase® are anonymized, but they are still to be considered sensitive due to the nature of the data.

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). Transfer of sensitive data to a third party is generally prohibited subject to limited exceptions explicitly stated in applicable legislation.

As the controller of the Data, the user shall be liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

Non-permitted use of VigiBase® Data includes, but is not limited to:
- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from UMC must include a statement:
(i) regarding the source of the information
(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
(iii) that the information does not represent the opinion of the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase®.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.

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Introduction of an electronic system for reporting adverse drug reactions in Tanzania

Kissa W Mwamwitwa and Adam M Fimbo, Tanzania Food and Drugs Authority (TFDA)

A ceremony that launched an electronic system for reporting Adverse Drug Reactions (ADRs) was inaugurated by the Minister for Health, Community development, Gender, Elderly and Children, Hon Ummy Ally Mwalimu, in Tanzania on 12 October 2016. This was a flagship event for the Tanzania Food and Drugs Authority (TFDA), marking its ongoing efforts to monitor medicines safety.

Honourable Ummy Ally Mwalimu, Minister for Health, Community Development, Gender, Elderly and Children (far left), Tanzania and Mr Hiiti B Sillo; observing the screen displaying one of interfaces of e-reporting tool for ADRs, during the launch ceremony, held at TFDA HQ on 12 October, 2016.

Traditionally, structured 'yellow forms' are used to report suspected ADRs in the country. This was first introduced in 1989. Inadequate number of reported ADRs has been considered the highest limitation, deterring timely and evidence-based decision making. The TFDA therefore decided to introduce the new electronic or e-reporting system to complement the existing spontaneous reporting system through yellow forms, and provide more channels for reporters to report. Both health-care workers and patients can send ADR reports directly to TFDA through the link www.tfda.go.tz/adr, which can be accessed using a PC connected to the internet or through a smart phone application. The establishment of an e-reporting system is a measure of success for the TFDA and is thought that it will be a 'game changer' in improving future number and rates of ADR reports in Tanzania.

The web-based programme was designed by the College of Informatics and Virtual Education (CIVE), the University of Dodoma (Tanzania). Advice on the ICH E2B format shared by the WHO Collaborating Centre (WHO CC) for International Drug Monitoring in Uppsala (Uppsala Monitoring Centre, UMC), was used to develop the tool and financial support was provided by the Tanzania Communications Regulatory Authority (TCRA). The programme allows data to be transferred into the WHO International Database of suspected adverse drug reactions, VigiBase®, by uploading the XML file in the user's VigiFlow[1] web-page. The software acts as a local database and shortens the time for data entry into VigiFlow.

Reporting of ADRs electronically will now be a key topic of discussion in all forthcoming sensitization and pharmacovigilance (PV) activities in Tanzania. TV, radio, newsletter advertisements, cartoons, short messages and social media will be used to advocate the e-reporting system and help ensure the system is well known throughout the country. The authority is enthusiastic about improving the PV system and the current priority is to increase the number of ADR reports.

The TFDA would like to acknowledge the continued support from the WHO and WHO CCs in strengthening PV activities, particularly the UMC for sharing the ICH E2B formatting guidelines.

Third WHO Asia Pacific Pharmacovigilance Training Course

The UMC and the JSS University in India have organized and led the third PV training course in the Asia Pacific region from 16 to 27 January 2017 in the city of Mysuru, Karnataka, India.

The JSS College of Pharmacy is a constituent college of JSS University. The JSS College of Pharmacy, in collaboration with JSS Hospital, is the southern regional training and technical support centre to Pharmacovigilance Program of India (PvPI). The JSS College of Pharmacy is the first to offer a Master's Programme in Pharmacy Practice and post graduate diploma in PV in the country, and is globally recognized and certified by the Accreditation Council for Pharmacy Education (ACPE), USA.

The UMC is the first WHO CC to be established for PV in 1978. The UMC provides technical support and guidance to National Centres in PV practice. UMC is experienced in running PV training courses, and has been organizing annual courses each year in Uppsala for nearly 20 years.

[1] VigiFlow is a web-based Individual Case Safety Report management system that is available for use by national pharmacovigilance centres of the WHO Programme for International Drug Monitoring. It is compliant with the international ICH E2B standard and maintained by the WHO Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre, Uppsala, Sweden.

The programme at Mysuru was interactive and consisted of lectures and hands on training in technical aspects of PV. A management component to help participants improve capacity to influence sustainable change in countries was also included. Participants from the Asia Pacific region and other regions (Africa, Europe and the Americas) attended the course. Participants came from: Afghanistan, Bangladesh, Guyana, India, Indonesia, Myanmar, Nepal, Sierra Leone, South Africa, Sri Lanka, Sudan, Sweden, and Zimbabwe. The course was aimed at developing PV knowledge and skills. It focused on PV best practices, signal detection, regulatory aspects, reporting culture, PV in public health, benefit/harm assessment and PV tools.

Recommendations from the 39th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring

The annual meeting of National Pharmacovigilance Centres (NPCs) participating in the WHO Programme for International Drug Monitoring (PIDM) provides a platform for representatives from around the world to meet and discuss pharmacovigilance (PV) issues. Representatives of Member States have the opportunity to interact with WHO and WHO CCs face to face, exchange information on country needs, and propose how WHO and WHO CCs can support them. One of the most important outcomes from this meeting is the formation of recommendations which shape the direction of future PV activities. Recommendations are made by delegates through group work. The thirty-ninth annual meeting of representatives of NPCs participating in the WHO PIDM was held from 14 to 17 November 2016, in Muscat, Oman. The meeting included eight working groups that discussed various issues in PV. The summary of discussions and the recommendations are described in this article.

Selection of topics for working groups at the WHO annual meeting of National Pharmacovigilance Centres

The format of the WHO National Pharmacovigilance Centres meeting is structured into four components: plenaries, group exercises (working groups), tutorials and update sessions. The topics of these meetings are proposed by Member States at the end of the annual meeting for National Pharmacovigilance Centres. WHO then distributes a questionnaire with the proposed topics to all Member States participating in the programme during the first quarter of every year. By completing the questionnaire topics can be prioritised to fit country's requirements ensuring the forthcoming meeting agenda has a good mix of subjects that are of interest and relevance in both advanced and resource limited settings.

Generation of Recommendations

The annual meetings of National Pharmacovigilance Centres usually have eight working groups, that run in parallel on two days. Delegates are provided with a list of objectives and expected outcomes prior to the working groups. During these sessions, a moderated discussion is conducted and attendees formulate and agree on a list of recommendations that are specifically targeted at WHO, WHO CCs and/or the National Pharmacovigilance Centres. A rapporteur is delegated from amongst the workshop participants and recommendations are then presented to the whole delegation in a plenary session. Following this, recommendations are finalized and confirmed.

***Working group one*: Defining the pharmacovigilance research question for countries: how do we go about it**

Moderators: P Nyambayo[2], S Varughese[3]

At the start of the session representatives in the group shared research areas of interest with each other. During discussions, key issues to keep in mind whilst identifying research topics were listed. These included research priorities, availability of resources and defining the research question. The working group identified basic research areas that all NPCs would benefit from. Such areas include, burden of ADRs, drug utilization studies and periodic assessment of national PV systems. In addition, the international PV network can also benefit from research that focuses on local issues but could have global indications. It was noted that amongst the countries represented in the working group a substantial amount of research has been conducted collectively. In addition, there is an abundance of PV data which have been collected through a variety of methods (active surveillance, electronic health care records, spontaneous reporting).

Recommendations from working group one: Defining the pharmacovigilance research question for countries: how do we go about it

For WHO CCs and WHO:

- WHO and/or WHO CCs should develop a portal/repository (research database) for sharing information on concluded and ongoing research and the methodologies used in undertaking these researches.

For National Pharmacovigilance Centres:

- Research is key in PV, especially when trying to communicate benefit and risks. It is important that such communication is backed by sound research.
- National Centres should define their research focus based on their priorities and available resources (human, financial, etc.).
- National Centres should periodically assess their PV systems and undertake impact studies that may be relevant to assessing the system.
    - Baseline burden of ADR morbidity and mortality in countries where such data are not available: This will help Centres measure the impact of subsequent PV interventions. It will also strengthen the case for PV when advocating to policy makers on the need to support PV activities.
    - Drug utilization studies: To help make sense of signals generated through the spontaneous reporting system. In addition, countries should make efforts to obtain information on the background incidence of ADRs of interest as this will further strengthen any signal generated by the system.

***Working group two*: Pharmacovigilance communication campaigns: how to measure impact**

Moderators: P Bahri[4], A Al Harbi[5]

The workshop started with examples of communication campaigns that have been conducted in various countries, such as weekly TV programmes in Oman, research on communication in Canada an ADR reporting campaign in Italy, health-care professional questionnaire in Armenia, radio programme and phone jingles in Nigeria, and TV crisis management in Belarus. The group considered how to evaluate the impact of these campaigns and devised elements that should be factored into a plan to assess the impact of communication campaigns.

[2] *Priscilla P M Nyambayo, Head-PV, Clinical Trials Division, Medicines Control Authority, Zimbabwe*
[3] *Shirley Varughese, Section Head, Central Drug Information, Ministry of Health, Oman*
[4] *Priya Bahri, Principle Scientific Administrator, European Medicines Agency (EMA)*
[5] *Ahmed Saif Al Harbi, Directorate General of Pharmaceutical Affairs, Ministry of Health, Oman*

Recommendations from working group two: Pharmacovigilance communication campaigns: How to measure impact

For WHO, WHO CCs and National Pharmacovigilance Centres:

- Develop communication impact evaluation methods and framework.
- Draw on existing health communication evaluation guidelines and involve professional public health evaluators from WHO expert pool.
- Share experiences of evaluating impact of communication, e.g. in WHO Pharmaceuticals Newsletter, a database/repository of communication materials/list of URLs, or a Facebook group.

For WHO and WHO CCs:

- Integration of evaluating communication interventions in the overall set of pharmacovigilance indicators for impact assessment.
- Follow-up at the national centres meeting in 2017 and at regional events.

Working group three: What people want from pharmacovigilance: what is your big question

Moderators: J Cook[6], M Al Maskari[7]

The objective of this working group was to discuss and share the expectations and major drivers of pharmacovigilance in various settings. The group sought to understand individual versus national needs. A list of common questions and expectations across resource settings were formulated. Common solutions and approaches were examined and the role of work-sharing was explored. Ideas were categorized into four themes which were: how do NPCs improve reporting; what should NPCs do with the information generated from ADR reports; how should NPCs share information effectively; and how do NPCs provide effective information to the public on pharmacovigilance and the benefits and risks of medicines and vaccines?

Recommendations from working group three: What people want from pharmacovigilance: what is your big question

For WHO and WHO Collaborating Centres:

Recommendations on improving reporting

- Evaluation of current incentive and mandatory reporting schemes and effectiveness of increasing reporting to assist national centred in instituting evidence-based schemes to increase reporting.
- Investigate effectiveness of a National Policy/Plan and mechanisms for this to be instituted as a health system performance measure.

Recommendations on information generated from ADR reports

- Investigate how to collect and make available 'safety knowledge', rather than just ADR data for use by pharmacovigilance centres.

Recommendations on sharing information effectively

- Stock-take of countries with information or work-sharing in place, identify barriers and enablers.
- Review use of Vigimed and how usage could be improved.

Recommendations on providing effective information to the public

- What is the evidence-base that better-informed patients result in better and safer use of medicines? How could this be used by countries to enhance their pharmacovigilance efforts?
- Collect examples of effective engagement with the public in different situations as resource for pharmacovigilance centres.

[6] *Jane Meredith Cook, Head, Pharmacovigilance and Special Access branch, Therapeutic Goods Administration, Australia*
[7] *Madiha Almaskari, Ministry of Health, Oman*

For pharmacovigilance centres:

Recommendations on improving reporting

- Trialling new educational methods with health-care professionals.
- Work with other areas e.g. Health-care facility accreditation.
- Consider hotlines and apps to support public reporting.

Recommendations on information generated from ADR reports

- Increase use of Vigimed.
- Consider use of VigiBase® for generating database sufficient for statistical analysis where a countries is not sufficient demographics and combined international data may not be as relevant – such as combining counties with similar population.

Recommendations on sharing information effectively

- Consider whether sharing of information is possible – legal or other barriers.
- Identify information sharing opportunities with other NPCs.

Recommendations on providing effective information to the public

- Identify methods being used and what could be added.

***Working group four*: Solutions to improve approaches, and enhance consumer reporting**

Moderator: L Härmark[8]

Strategies to enhance the participation of consumers as reporters were discussed during the workshop. Two strategies were proposed: 1) to focus on creating a culture of reporting as a necessary first step towards patient reporting through awareness creation and education of the general public, 2) reporting tools and media should be well coordinated and made accessible and easy to complete by the consumer.

Recommendations from working group four: Solutions to improve approaches, and enhance consumer reporting

For WHO and WHO CCs:

- To facilitate the rebranding of pharmacovigilance for the public.
- To offer technical guidance to national pharmacovigilance centres to simplify ADR reporting tools and help make these tools accessible and easy to complete.

For National Pharmacovigilance centres:

- To decentralize pharmacovigilance awareness and education campaigns by using regional and district offices, if available, to help facilitate the creation of awareness of consumer reporting.
- To collaborate with other key organizations to facilitate education and creation of awareness of ADRs, how to recognize and report them when they occur.
- To utilize Information, Communication, and Education (ICE) materials as a means to widely disseminate ADR educational literature to the general public.
- To research consumer reporting medium preference and to target reporting tools and pharmacovigilance messaging based on the reporter preference.

[8] *Linda Harmark, Head of Innovation and Projects, Netherlands Pharmacovigilance Centre Lareb, Netherlands*

***Working group five*: What to teach pharmacovigilance beginners**

Moderators: S Olsson[9], H Al-Ramimmy[10]

The objective of this working group was to adapt the WHO-International Society of Pharmacovigilance (ISoP) PV curriculum[11] for teaching pharmacovigilance to beginners. The WHO-ISoP PV curriculum consists of an exhaustive number of topics, and ideally a course should be tailored to meet the specific needs of the audience. During the workshop, participants discussed what is meant by the term 'PV beginner', and agreed for this workshop that a PV beginner is a person who graduates in PV or has other qualifications but who will/or is beginning to work in PV. The group reviewed each of the topic headings in the PV modules and decided whether topics should be included in PV training for beginners and agreed on a set of topics. It was emphasized that the list of topics selected from the WHO-ISoP curriculum for teaching PV to beginners is a starting point, and is subject to change. It should be treated as a suggestion rather than a recommendation.

Conclusions from working group five: What to teach pharmacovigilance beginners
Topics suggested to be included in PV courses for beginners:

1. ***What is and why do we need pharmacovigilance?***
   - Subject and scope of PV
   - History of PV: important ADRs, methods and organizational developments
   - ADRs and public health
   - Limited risk prediction from molecular analogy, pre-clinical studies and pre-marketing clinical trials
2. ***Fundamental Clinical Aspects of ADRs***
   - Types and mechanisms of ADRs; Non-genetic risk factors for ADRs and complex interactions
3. ***Important ADRs and 'Risk Driving' ADRs of Important Medicines***
4. ***Individual Case Safety Reports***
   - Concerns about ADRs: medical, psychological and regulatory background and reasons for reporting
   - Contents, structure and validity of reports and reporting procedures
   - Case assessment
5. ***Counterfeiting, demarcation against manufacturing-related quality defects***
   - Counterfeiting, demarcation against manufacturing-related quality defects
   - Medication error: definition, impact, detection
6. ***Spontaneous ICSR Reporting Systems***
   - Definition, settings, potential and limitations of systems
   - Data transmission and entry
   - Data retrieval
7. ***Signal Detection and Management***
   - Definition of a signal
   - Sources, potential, detection by non-statistical medical means
8. ***Benefit-Risk Assessment - 'Benefit-risk': definitions***
9. ***Pharmacovigilance and Risk Management Systems: definition, stakeholders and operation***
   - Pharmacovigilance systems: definition, stakeholders and operation
10. ***Industry and Regulatory Authorities, Mandatory Procedures from Legislation***
11. ***PV Organisation and Public Health***
    - Detection, documentation and reporting of ADRs at the local level
    - Public Health and stake holders, e.g. other PV projects, international organizations and industry associations
12. ***Communication***
    - Context and guidance
    - Communication with patients and health-care professionals: tools, channels and processes
    - Communication with patients and health-care professionals: contents and presentation
13. ***Sources of Information***
    - Primary data: figures, facts, terms, cases
    - Secondary information: assessments, judgements, decisions (hardcopy or electronic version)
    - Electronic/Internet methods for searching and managing information
    - Materials and training courses, where appropriate, specific for regions or settings
    - 'Hands-on' practical training is essential.

[9] *Sten Olsson, WHO Programme Expert, Uppsala Monitoring Centre*
[10] *Hussain Talib Tahni Al Ramimmy, Ministry of Health, Oman*
[11] *ISoP (International Society of Pharmacovigilance) curriculum (Teaching Pharmacovigilance: the WHO-ISoP Core Elements of a Comprehensive Modular Curriculum). http://isoponline.org/training/pv-curriculum/*

***Working group six*: Why and when do we undertake cohort event monitoring?**

Moderators: A Dodoo[12], L Härmark

The objective of this working group was to share current experiences and lessons learnt with Cohort Event Monitoring (CEM) in countries. Experiences of CEM studies in Ghana, Nigeria, and the Netherlands were shared. All three experiences faced the common challenge of recruiting subjects in the cohort, building software adaptable to many types of studies, obtaining good data quality and ability to analyse data. The working group discussed situations that best suit CEM method. Centres should do CEM when checking a new product to clarify safety and lack of harm, to confirm or clarify a good safety profile and/or confirm lack of harm.

Recommendations from working group six: Why and when do we undertake cohort event monitoring?

For WHO and WHO CCs:

- Review and update WHO CEM guidelines based on the experience of implementing countries.
- Provide training on how to design a CEM study.
- Provide a better understanding of the resources required and available to countries using CEM.
- Provide guidance on how reports of AEs from a CEM study should be transferred to a national database and VigiBase®.

For National Pharmacovigilance Centres:

- When considering a CEM study, consider the information needed to answer a specific question and whether CEM is the most appropriate method (CEM is expensive and time consuming – and is not always feasible).
- Take into account the resources required and resources actually available.
- When conducting CEM write a study protocol and have it assessed according to local rules and regulations.

***Working group seven*: Herbal-drug interactions**

Moderator: S Skalli[13], S Al Jabri[14]

Representatives discussed experiences and challenges faced in evaluating and monitoring interactions between herbal and other medicine. The working group discussed challenges such as the lack of regulation of herbal remedies, variability in herbal medicines composition, concerns about substandard and falsified herbal products. Various tools to support detection of herb-drug interactions were considered.

Recommendations from working group seven: herbal-drug interactions

For WHO and WHO CCs:

- To provide guidance on implementing an expert committee for herbal medicines and herbal drug interaction.
- To guide and support herbal drug interaction campaigns, workshops, trainings and e-learning.
- To support countries to improve reporting from health professionals and consumers.

[12] *Alex Dodoo, WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance, Ghana*
[13] *Souad Skalli, Head of Pharmacovigilance of Herbal Medicines Unit, Centre Anti Poison et de Pharmacovigilance du Maroc WHO Collaborating Centre, Morocoo*
[14] *Sharifa Al Jabri, Head of Quality Assurance and Medication Safety, DGPA&DC, Ministry of Health, Oman*

- To encourage countries, particularly China (Traditional CM products) and India (AYUSH products) to report ADR and herbal drug interactions, substandard and falsified products to the WHO global database, VigiBase®.
- To harmonize terminologies of herbal medicines terms (manuals).
- To promote integration of herbal medicine interaction monitoring in public health programmes.
- To support and help the set up herbal-PV activities in PV centres.
- To update WHO herbal pharmacovigilance guidelines (last updated in 2004).
- To provide technical support to countries to detect and monitor herbal drug interaction signals, obtain sufficient information (number, information completeness, number of countries that report, Herbal specificities) and develop VigiBase® for optimal identification of signals of herbal-adverse events and herbal drug interactions.
- To share experience of safety of herbal products via a common platform (e.g. Vigimed or others).
- To share the experience of WHO-CC in Rabat in this area of work.

For National Pharmacovigilance Centres:

- Consider safety monitoring of herbal drug interactions as a component of PV.
- Obtain regulatory status for herbal medicines, herbalists and traditional practitioners.
- Collaborate with institutions that conduct research and teach herbal and traditional medicines, for the integration of PV of herbal medicines and herbal drug interaction in the curriculum of health-care professionals and in public health programmes.
- Plan to establish herbal medicine monographs.
- Commit reports of suspected ADRs with herbal medicine use and herbal drug interaction to VigiBase®.

***Working group eight*: Statistical methods in pharmacovigilance**

Moderators: N Norén[15], R Al Sabri[16]

The objective of this working group was to identify different needs for statistical methods in pharmacovigilance at NPCs. During the session, participants worked together to form a list of suggestions on how to support decision-making for signals, how to prioritise output from a statistical method if too many combinations are detected, how to identify region-specific safety signals, how to select which reports to review, and how to identify product quality issues. They agreed that clinical review and causality assessment remain most important while aggregate statistics such as disproportionality measures may be required by some 'upstream' decision-makers.

Recommendations from working group eight: Statistical methods in pharmacovigilance

For WHO and WHO CCs:

- To evaluate whether a minimum database size and heterogeneity can be identified for given methods, for example, to identify when disproportionality analysis is relevant.

For National Pharmacovigilance Centres:

- Consider clinical review and causality assessment as the most important components of decision-making for signals.

[15] *Niklas Norén, Chief Science Officer, Uppsala Monitoring Centre*
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