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WHO Vision for Medicines Safety
No country left behind: worldwide pharmacovigilance for safer medicines, safer patients

The aim of the Newsletter is to disseminate regulatory information on the safety 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 safety of medicines and legal actions taken by regulatory authorities around the world. It also provides signals based on information derived from the WHO global database of individual case safety reports, VigiBase.

This newsletter also includes the Recommendations from the 41st Annual Meeting of Representatives of the National Pharmacovigilance Centres Participating in the WHO Programme for International Drug Monitoring.

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Aluminium potassium sulfate hydrate/tannic acid

Risk of anaphylaxis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for aluminium potassium sulfate hydrate/tannic acid (Zione Injection®) should be revised to include anaphylaxis as an adverse drug reaction.

Aluminium potassium sulfate hydrate/tannic acid is indicated for prolapsed internal haemorrhoids.

Six cases involving anaphylaxis have been reported in patients treated with aluminium potassium sulfate hydrate/tannic acid in Japan during the previous three fiscal years. For five of the six cases a causal relationship with the product could not be ruled out.

MHLW/PMDA concluded that the revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 27 November 2018 *(www.pmda.go.jp/english/)*

Asunaprevir and daclatasvir

Risk of renal impairment

Japan. The MHLW and the PMDA have announced that the package inserts for asunaprevir (Sunvepra®), and preparations containing daclatasvir (Daklinza® and Ximency®) should be revised to include renal impairment as an adverse drug reaction.

Asunaprevir and daclatasvir are indicated for the improvement of viremia in patients with chronic hepatitis C serogroup 1 or with compensated cirrhosis type C serogroup.

18 cases of renal impairment have been reported in patients who took asunaprevir or daclatasvir in Japan during the previous three fiscal years. In five of these cases a causal relationship with the product could not be excluded.

The MHLW/PMDA concluded that the revision of the package inserts was necessary based on the results of the investigation of the currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 10 January 2019 *(www.pmda.go.jp/english/)*

Atorvastatin and antivirals: interaction

Increase in atorvastatin plasma levels

Egypt. The Egyptian Pharmaceutical Vigilance Center (EPVC) has announced that the product information for atorvastatin will be updated to include a warning about the potential increase in atorvastatin levels when co-administered with elbasvir/grazoprevir and glecaprevir/pibrentasvir. The combined use of glecaprevir/pibrentasvir with atorvastatin is now contra-indicated.

Atorvastatin is a synthetic lipid-lowering agent indicated for the prevention of cardiovascular diseases and hypercholesterolaemia. Elbasvir/grazoprevir and glecaprevir/pibrentasvir preparations are indicated for the treatment of hepatitis C (HCV).

Risk of myopathy may be increased with the concomitant use of atorvastatin and antivirals for treatment of HCV.

Reference:
Newsletter, EPVC, December 2018 *(www.epvc.gov.eg)*

Axitinib

Risk of interstitial lung disease

Japan. The MHLW and the PMDA have announced that the package insert for axitinib (Inlyta®) should be revised to include interstitial lung disease as an adverse drug reaction.

Axitinib is indicated for the treatment of unresectable metastatic renal cell carcinoma.

A total of 20 cases involving interstitial lung disease have been reported in patients treated with axitinib in Japan during the previous three fiscal years. A causal relationship with the product could not be excluded in two of these cases.

MHLW/PMDA concluded that the revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 10 January 2019 *(www.pmda.go.jp/english/)*

Calcitriol injection

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for the injectable form of calcitriol (Rocaltrol Injection®) should be revised to include shock and anaphylaxis as adverse drug reactions.

Calcitriol is indicated for secondary hyperparathyroidism in patients undergoing maintenance renal dialysis.

A total of four cases involving shock or anaphylaxis have been reported in patients

treated with injectable calcitriol in Japan during the previous three fiscal years. A causal relationship with the product could not be ruled out in one of the cases.

MHLW/PMDA concluded that the revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 27 November 2018 *(www.pmda.go.jp/english/)*

Denosumab

Risk of new primary malignancy (NPM)

Singapore. The Health Sciences Authority (HSA) has announced that the package insert for denosumab (Xgeva®) is in the process of being updated to include the incidence of new primary malignancy (NPM) as an adverse reaction.

Denosumab is a human monoclonal antibody (IgG2) indicated for the prevention of skeletal related events (e.g. pathological fracture and spinal cord compression).

During a routine review of denosumab in February 2018, the European Medicines Agency (EMA) noted that NPM was reported more frequently in patients with advanced bone malignancies treated with denosumab compared to zoledronic acid. Although the absolute differences in event rates were small and a clear causal mechanism has not been identified, the EMA could not exclude that there is a potential mechanism linked to an impaired immune response with the use of denosumab.

The HSA has not received any national adverse event reports for NPM associated with the use of denosumab.

Reference:
Product Safety Alerts, HSA, 28 December 2018 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.4, 2018: Risk of new primary malignancies in UK)

Direct-acting antivirals for chronic hepatitis C

Risk of hypoglycaemia in patients with diabetes

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) is updating the Summary of Product Characteristics and Patient Information Leaflets for direct acting antivirals (e.g. daclatasvir (Daklinza®), sofosbuvir/velpatasvir (Epclusa®) and ledipasvir/sofosbuvir (Harvoni®)), to include safety advice to minimise the risk of hypoglycaemia in patients taking medicines for diabetes.

Studies show that some diabetic patients, initiating direct-acting antiviral therapy for chronic hepatitis C infection, have experienced hypoglycaemia. This was confirmed in an EU review.

Glucose levels should be monitored closely in patients with diabetes during direct-acting antiviral therapy for hepatitis C and medicines should be modified when necessary.

Reference:
Drug Safety Update, MHRA, 18 December 2018 (*www.gov.uk/mhra*)

(See WHO Pharmaceuticals Newsletter No.2, 2018: Possible effects on blood glucose control when used in patients with type 2 diabetes in New Zealand; No.2, 2017: Possible effects on blood glucose control when used in patients with type 2 diabetes: added to the medicine monitoring scheme in New Zealand)

Emollients

Risk of severe and fatal burns

United Kingdom. The MHRA has announced that the outer packaging and product containers for paraffin-based emollients should include fire hazard warnings. The Summary of Product Characteristics will also be updated to include warnings about the risk of severe and fatal burns.

Patients who use paraffin-based emollients, regardless of the paraffin concentration, should not smoke or go near naked flames because clothing or fabric such as bedding or bandages that have been in contact with an emollient or emollient-treated skin can rapidly ignite.

Emollients are an important and effective treatment for chronic dry skin conditions. The emollient products are not flammable, but they can increase the speed of ignition and intensity of fire if fabric containing dried residue is ignited.

The MHRA is aware of 11 cases in which paraffin-based emollients are suspected to have contributed to an increase in the speed and intensity of a fire, resulting in fatal burns injury. There are also 50 fire incidents (49 fatal) reported by Fire and Rescue Services across the UK between 2000 and November 2018, but in most of these it is not clear what the attributable role of paraffin creams were in the deaths.

Reference:
Drug Safety Update, MHRA, 18 December 2018 (*www.gov.uk/mhra*)

(See WHO Pharmaceuticals Newsletter No.3, 2013: May cause skin irritation, particularly in children with eczema in UK)

Fluoroquinolone antibiotics

1. Risk of tendon damage and neuropathies

Ireland. The Health Products Regulatory Authority (HPRA) has updated the Summary of Product Characteristics (SmPC) and Package Leaflets (PL) for all fluoroquinolone antibiotics to include tendonitis, tendon rupture, neuropsychiatric effects and neuropathies associated with paraesthesia as adverse reactions. The update followed conclusions from a recent review by EMA's Pharmacovigilance Risk Assessment Committee (PRAC)'s.

Fluoroquinolones are a class of broad spectrum antibiotics and include ciprofloxacin, levofloxacin, ofloxacin and moxifloxacin.

The PRAC recommended that fluoroquinolone antibiotic use should be further restricted, and the information provided to patients on potential adverse reactions should be expanded to emphasize the possibility of persisting effects.

Reference:
Drug Safety Newsletter, HPRA, December 2018 *(www.hpra.ie)*

(See WHO Pharmaceuticals Newsletter No.6, 2018: Risk of long-lasting and disabling effects in Europe; No.4, 2018: Strengthened warnings on the risk of hypoglycaemia and mental health adverse effects in USA; No.2, 2017: Potential risk of persistent and disabling side effects in Canada; No.1, 2017: Risk of retinal detachment in Singapore; No.5, 2016: Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system in USA; No.3, 2016: Restricting use in USA; No.1, 2016: Risk of retinal detachment in Canada)

2. Risk of aortic aneurysm and aortic dissection

Japan. The MHLW and the PMDA have announced that the package inserts for fluoroquinolones (e.g. moxifloxacin (Avelox®), levofloxacin (Cravit®), ofloxacin (Tarivid®)) should be revised to include aortic aneurysm and aortic dissection as adverse drug reactions.

Results of several epidemiological studies and a non-clinical study have suggested an association between fluoroquinolone use and development of aortic aneurysm or aortic dissection.

Although no cases involving aortic aneurysm or aortic dissection have been reported in Japan during the previous three fiscal years, MHLW/PMDA concluded that revision of the package inserts was necessary based on the opinions of the expert advisors.

Patients should be carefully monitored and instructed to seek medical attention immediately if they experience symptoms such as pain in the abdomen, chest or back. Imaging assessment should be considered if necessary, for patients at risk.

Reference:
Revision of Precautions, MHLW/PMDA, 10 January 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.6, 2018: Potential risk of aortic aneurysm and dissection in UK)

Hydrochlorothiazide

Risk of non-melanoma skin cancer

Egypt. The EPVC has announced that the Summary of Product Characteristics and Package Leaflet for hydrochlorothiazide will be updated to include the risk of non-melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma) as an adverse reaction.

Hydrochlorothiazide is widely used to treat hypertension, cardiac, hepatic and nephrogenic oedema or chronic heart insufficiency.

Pharmacoepidemiological studies have shown an increased risk of non-melanoma skin cancer with exposure to increasing cumulative doses of hydrochlorothiazide.

Patients taking hydrochlorothiazide should be informed of the risk and advised to regularly check their skin. Also, patients should be advised to limit exposure to sunlight and UV rays, and suspicious skin lesions should be examined, potentially by performing histological examinations of biopsies.

Reference:
Newsletter, EPVC, December 2018 *(www.epvc.gov.eg)*

(See WHO Pharmaceuticals Newsletter No.6, 2018: Risk of non-melanoma skin cancer in UK)

Hydrocortisone (muco-adhesive buccal tablets)

Risk of insufficient cortisol absorption and life-threatening adrenal crisis

United Kingdom. The MHRA has updated the product information for hydrocortisone muco-adhesive buccal tablets, to include warnings about the serious risks associated with off-label use for the treatment of adrenal insufficiency in children. Adrenal insufficiency can potentially occur due to insufficient cortisol absorption which can lead to adrenal crisis in stress situations.

Hydrocortisone muco-adhesive buccal tablets are indicated only for local use in the mouth for aphthous ulceration (mouth ulcers).

There are oral formulations of hydrocortisone authorized for the treatment of adrenal insufficiency. Prescribers and pharmacists should only use the licensed products.

Reference:
Drug Safety Update, MHRA, 18 December 2018 *(www.gov.uk/mhra)*

Infliximab

Risk of mycosis fungoides

Australia. The Therapeutic Goods Administration (TGA) has announced that product information for infliximab (Remicade®) is being updated with new information relating to mycosis fungoides.

Infliximab is indicated for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, Crohn's disease and ulcerative colitis.

The TGA identified a safety signal based on three local reports of adverse events. The number of observed reports of mycosis fungoides with the use of infliximab is higher than expected. After further analysis of the signal, the TGA is working with the sponsor of infliximab to add information about this condition to the adverse effects section of the product information.

Reference:
Medicines Safety Update, TGA, Vol. 9, No. 4, December 2018 (*www.tga.gov.au*)

(See WHO Pharmaceuticals Newsletter No.4, 2018: Potential risk of linear IgA bullous dermatosis in Canada; No.6, 2015: Limited evidence: risk of cancer (lymphoma, hepatosplenic T-Cell lymphoma, and leukaemia) in Canada; No.5, 2015: Risk of non-melanoma skin cancers, particularly in psoriasis patients in Australia)

Lenalidomide

Risk of progressive multifocal leukoencephalopathy (PML)

Japan. The MHLW and the PMDA have announced that the package insert for lenalidomide (Revlimid®) should be revised to include progressive multifocal leukoencephalopathy (PML) as an adverse drug reactions.

Lenalidomide is indicated for the treatment of multiple myeloma, myelodysplastic syndrome associated deletion 5q cytogenetic abnormality and relapsed or refractory adult T-cell leukemia/lymphoma.

There were no cases of PML reported in patients treated with lenalidomide in Japan in the previous three fiscal years. Three cases have been reported overseas, and MHLW/PMDA have concluded that the revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Patients should be closely monitored during and after the administration of lenalidomide. If symptoms such as disturbed consciousness, cognitive disorder, paralysis, or disorders related to linguistic capacity are observed, administration of this drug should be discontinued, diagnostic assessment using MRI and cerebrospinal fluid tests should be performed, and other measures should be taken as appropriate.

Reference:
Revision of Precautions, MHLW/PMDA, 10 January 2019 *(www.pmda.go.jp/english/)*

Nusinersen

Risk of hydrocephalus

Japan. The MHLW and the PMDA have announced that the package insert for nusinersen (Spinraza Intrathecal Injection®) should be revised to include hydrocephalus as an adverse drug reaction.

Nusinersen is indicated for the treatment of spinal muscular atrophy.

One case involving hydrocephalus has been reported in patients treated with nusinersen in Japan in the previous three fiscal years. A causal relationship with the product could not be excluded in this case.

MHLW/PMDA concluded that the revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 10 January 2019 *(www.pmda.go.jp/english/)*

(See WHO Pharmaceuticals Newsletter No.6, 2018: Potential risk of communicating hydrocephalus in UK)

Varicella vaccine (freeze-dried live attenuated)

Risk of aseptic meningitis

Japan. The MHLW and the PMDA have announced that the package insert for freeze-dried live attenuated varicella vaccine (Biken®) should be revised to include aseptic meningitis as an adverse reaction.

Freeze-dried live attenuated varicella vaccine is indicated for prevention of varicella and herpes zoster in patients aged 50 years and older.

A total of two cases of aseptic meningitis have been reported in patients vaccinated with freeze-dried live attenuated varicella vaccine in Japan during the previous three fiscal years. A causal relationship with the product could not be ruled out in one of the cases.

MHLW/PMDA concluded that the revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Reference:
Revision of Precautions, MHLW/PMDA, 27 November 2018 *(www.pmda.go.jp/english/)*

Vascular endothelial growth factor receptor tyrosine kinase inhibitors

Risk of artery dissections

and artery aneurysms

Canada. Health Canada is working with manufacturers to update the product safety information for vascular endothelial growth factor receptor tyrosine kinase inhibitors (VEGFR TKIs) on the risk of artery dissections/artery aneurysms.

VEGFR TKIs are indicated for the treatment of various types of cancer, including kidney, liver and soft tissue cancers. There are currently eight VEGFR TKIs marketed in Canada: sunitinib (Sutent®), sorafenib (Nexavar®), axitinib (Inlyta®), pazopanib (Votrient®), ponatinib (Iclusig®), regorafenib (Stivarga®), vandetanib (Caprelsa®) and lenvatinib (Lenvima®).

Health Canada had received one Canadian report of artery dissection and one Canadian report of artery aneurysm with the use of VEGFR TKIs. Also, Health Canada looked at 208 international reports of artery dissections/artery aneurysms suspected to be linked to the use of VEGFR TKIs. Health Canada's review concluded that there may be a link between the use of VEGFR TKIs and artery dissections/artery aneurysms.

Reference:

Summary Safety Review, Health Canada, 3 December 2018 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals NewsletterNo.1, 2015: Thrombotic microangiopathy in Canada)

Azithromycin

Risk of haematological relapses

Singapore. The HSA has announced that a clinical trial, investigating effectiveness of long-term azithromycin to prevent bronchiolitis obliterans syndrome (BOS) in certain haematological patients, was terminated prematurely because of an increase in the rate of haematological malignancy relapses and mortality in patients that had a haematopoietic stem cell transplantation (HSCT).

Azithromycin is a macrolide antibiotic. It is not approved for the prophylaxis of BOS in HSCT patients. There are 15 generic azithromycin-containing products registered in Singapore.

The aim of the clinical trial was to investigate if early administration of azithromycin could improve airflow decline-free survival two years after allogeneic HSCT.

The trial investigators concluded that early administration of azithromycin for prophylaxis of BOS in HSCT patients resulted in worse airflow decline-free-survival than did placebo. However, the findings were limited by the early termination of the trial and further investigation was required.

Reference:
Product Safety Alerts, HSA, 28 December 2018 (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.6, 2018: Increased risk of cancer relapse in donor stem cell transplant patients in USA)

Beta-blocker, statins, selective serotonin re-uptake inhibitors and varenicline

Risk of parasomnias

New Zealand. Medsafe has announced that beta-blockers, statins, selective serotonin re-uptake inhibitors (SSRIs) and nicotine replacement therapies may cause various parasomnias.

Parasomnia is an umbrella term for complex movements or behaviours during sleep, including abnormal dreaming, nightmares (paroniria) and sleepwalking (somnambulism).

The Centre for Adverse Reactions Monitoring (CARM) received over 70 reports of various parasomnias over the past five years. The most frequently reported terms are abnormal dreams, paroniria and sleep disorder. Commonly reported medicines include statins, varenicline and montelukast.

Reference:
Prescriber Update, Medsafe, December 2018 (*www.medsafe.govt.nz/*)

(See WHO Pharmaceuticals Newsletter No.4, 2012: Continued reporting of abnormal sleep-related events and amnesia in Australia)

Erythropoietin

Risk of pure red cell aplasia

New Zealand. Medsafe has announced that pure red cell aplasia (PRCA) may occur after treatment with erythropoietin (Eprex®) in patients with chronic kidney disease.

Erythropoietin is an erythropoiesis-stimulating agent used to treat or prevent anaemia of varying origins.

The CARM received 11 case reports of PRCA after treatment with erythropoietin.

If PRCA is diagnosed, erythropoietin treatment must be discontinued immediately, and testing for erythropoietin antibodies should be considered. If antibodies to erythropoietin are detected, patients should not be switched to another erythropoiesis-stimulating agent because anti-erythropoietin antibodies cross-react with other erythropoiesis-stimulating agents.

Reference:
Prescriber Update, Medsafe, December 2018 (*www.medsafe.govt.nz/*)

Ferric carboxymaltose

Risk of hypophosphatemia

New Zealand. Medsafe has announced that ferric carboxymaltose (Ferinject®) may cause hypophosphatemia.

Ferric carboxymaltose is indicated for treatment of iron deficiency when oral iron preparations are ineffective or cannot be used. Hypophosphatemia is currently listed as a common adverse reaction in the data sheet for ferric carboxymaltose.

Symptomatic hypophosphatemia associated with the use of ferric carboxymaltose has been reported in the literature, and symptoms include: vertigo, nausea, general weakness, tingling in the hands and depression-like symptoms.

The mechanism for hypophosphatemia in relation to ferric carboxymaltose is unclear, but regulatory protein fibroblast growth factor 23 (FGF23) is thought to be involved. FGF23 is secreted by osteocytes and acts to increase the loss of phosphate through the kidneys. Administration of ferric carboxymaltose increases the amount of biologically active FGF23.

The CARM received five case reports of hypophosphatemia in association with parenteral iron treatment between February 2016 and April 2018.

Reference:
Prescriber Update, Medsafe, December 2018
(www.medsafe.govt.nz/)

Ipilimumab

Risk of colitis

United Kingdom. The MHRA has announced that colitis occurs commonly in patients treated with ipilimumab (Yervoy®).

Ipilimumab is an immune checkpoint inhibitor and indicated for the treatment of advanced (unresectable or metastatic) melanoma.

An European review identified a total of 40 global cases suggestive of gastrointestinal-associated cytomegalovirus (CMV) infection or reactivation with ipilimumab monotherapy or ipilimumab in combination with nivolumab. All cases of CMV gastrointestinal infection or reactivation occurred in patients with colitis that was refractory to corticosteroid treatment.

Health-care professionals should advise patients to contact their health-care professional immediately at the onset of symptoms of colitis, including diarrhoea, blood in stools or abdominal pain. If patients on ipilimumab present with diarrhoea or colitis, investigate possible causes, including infections; perform a stool infection work-up and screen for CMV.

Reference:
Drug Safety Update, MHRA, 9 January 2019
(www.gov.uk/mhra)

Sulfamethoxazole

Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): insufficient evidence

Canada. Health Canada has announced that its review concluded that there is not enough evidence at this time to establish a link between the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and the use of sulfamethoxazole containing products.

Sulfamethoxazole is used to treat a wide range of infections caused by bacteria.

Health Canada's review was triggered by a signal from the WHO global database for reports of adverse reactions which suggested DRESS was being reported at a higher rate than expected for sulfonamides.

Health Canada received four unique Canadian reports of DRESS that could be related to sulfamethoxazole use, and found a possible link between DRESS and sulfamethoxazole in two reports. Also, the review looked at five international reports of DRESS and two of them showed a possible link between DRESS and sulfamethoxazole use.

However, after looking at all the available evidence, Health Canada concluded that there is not enough evidence at this time to establish a link between the risk of DRESS and the use of sulfamethoxazole containing products, and that the safety information of the products is appropriate at this time.

Reference:
Summary Safety Review, Health Canada, 7 January 2019
(*www.hc-sc.gc.ca*)

Tapentadol

Risk of seizures and serotonin syndrome when co-administered with other medicines

United Kingdom. The MHRA has announced that tapentadol (Palexia®) may increase seizure risk in patients taking other medicines that lower seizure threshold, for example, antidepressants such as serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants and antipsychotics.

Tapentadol is an opioid analgesic indicated for the relief of acute, moderate to severe pain that can only be adequately managed with opioid analgesics in adults and children aged two years and older.

The risk of seizures is a recognized adverse drug reaction for all opioid medicines, but a recent review for tapentadol in the EU identified the need for strengthened advice about the risk of seizures. Approximately half of the identified spontaneous reports of seizures reflected co-administration of tapentadol with at least one other drug known to lower seizure threshold.

Also, MHRA is aware of reports of serotonin syndrome identified when tapentadol is co-administered with SSRIs, SNRIs, tricyclic antidepressants and antipsychotics.

Withdrawal of the serotoninergic medicine, together with supportive symptomatic care, usually brings about a rapid improvement. The continued use of tapentadol must be evaluated on an ongoing basis.

Reference:
Drug Safety Update, MHRA, 9 January 2019
(www.gov.uk/mhra)

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 reports of suspected adverse drug reactions available in the WHO global database of individual case safety reports (ICSRs), VigiBase. The database contains over 18 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. International pharmaceutical companies, when identified as uniquely responsible for the drug concerned, are invited to comment on the signal text. Signals are thereafter communicated to National Pharmacovigilance Centres, before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version. More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 24). 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. For more information, on the UMC Measures of Disproportionate Reporting etc., 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.

Levofloxacin and myoclonus in the elderly over 75 years: susceptibilities and prescribing issues

Sofia Zappacosta, Uppsala Monitoring Centre and Dr. Ruth Savage, New Zealand

Summary

Signal detection focusing on subgroups in VigiBase, the WHO global database of individual case safety reports (ICSRs), identified disproportionate reporting of the combination levofloxacin and myoclonus only in patients aged over 75 years. Product labels for levofloxacin do not list myoclonus as an adverse reaction and indicate that the listed central nervous system adverse effects are not confined to the elderly. Dose adjustments are recommended for levofloxacin in patients with renal impairment as it primarily undergoes renal excretion as the unchanged drug. Assessment of the 20 reports indicated that levofloxacin was the most likely cause of myoclonus in the majority of the cases. Co-reported central nervous system adverse effects included encephalopathy and seizures. Five patients had renal impairment with clear evidence of dose adjustment in one. There was a high prevalence of cerebral and metabolic disorders likely to predispose to myoclonus. In contrast, renal impairment and cerebral disorders were not prominent features in the 18 reports for patients aged under 75 years, which might explain why disproportionate reporting of the combination was confined to the elderly. Medicines that may also cause myoclonus were co-prescribed in 40% of the older group compared with 33% of younger patients and so were less likely to account for the observed age difference in reporting. Most of these medicines can also lower the seizure threshold, and product labels caution about the use of such medicines with levofloxacin. Reports of levofloxacin and myoclonus support a causal relationship for levofloxacin and myoclonus and indicate some possible reasons why the elderly may be more often affected. The reports also provide reminders to monitor renal function and adjust the levofloxacin dose accordingly, and to avoid, where possible, co-prescription of medicines with levofloxacin that can also induce myoclonus and lower the seizure threshold.

Introduction

A signal detection screening in VigiBase, the WHO global database of individual case safety reports (ICSRs) focusing on subgroups at risk identified disproportionate reporting of a combination of levofloxacin and myoclonus in the elderly population 75 years and older. As of 25 February 2018, the IC value for the elderly age group was 1.16 (IC_{025}: 0.05). However, the reporting was not disproportionate for all age groups combined.

Levofloxacin is a synthetic antibacterial agent of the fluoroquinolone class. It is indicated in adults for the treatment of diverse infections such as acute bacterial sinusitis, acute exacerbations of chronic bronchitis, community-acquired pneumonia, chronic bacterial prostatitis, pyelonephritis and complicated urinary tract infections.[1] Recommended daily doses range from 250 mg for uncomplicated urinary tract infections to 750 mg for more serious diverse bacterial infections according to the United States (US)

Food and Drug Administration (FDA) label,[1] while the United Kingdom (UK) Summary of Product Characteristics (SmPC) allows for 1000 mg daily for specific infections.[2]

The preferred route of administration is oral, showing a rapid and almost complete absorption after 1-2 hours and 99-100% bioavailability. It is excreted primarily as unchanged drug in the urine within 48 hours of administration, by tubular secretion in addition to glomerular filtration. In patients with impaired renal function (creatinine clearance < 50 mL/min), adjustment of the dose regimen, relative to the recommended dose for the indication, is necessary to avoid levofloxacin accumulation.[1]

Levofloxacin has been shown to penetrate a range of peripheral tissues[1] but it is believed that its penetration into cerebrospinal fluid (CSF) is poor.[3] In vitro and in vivo studies have suggested that the brain distribution of several quinolones is restricted by the operation of multiple efflux transporters.[4]

Fluoroquinolones are known to cause central nervous system (CNS) adverse effects such as hallucinations and seizures.[1] These effects are likely to be the result of excitation of N-methyl-D-aspartate (NMDA) receptors and inhibition of gamma-aminobutyric acid (GABA-A) receptors.[5]

Myoclonus is a neurological sign described as involuntary and sudden contractions of a muscle or group of muscles affecting the arms, legs, face, neck or other parts of the body, resulting in twitches or jerks. It can result in debilitating impairment for which specific treatment is needed.[6,7] Myoclonus is associated with a wide range of clinical conditions and can be of cortical, subcortical or spinal origin. There is therefore no specific age range that is typically affected. It can occur with both focal nervous system damage and metabolic disorders including renal failure, electrolyte abnormalities and hypoxia. It can occur with epilepsy, peripheral motor neuropathy and encephalopathy, all of which are recognised adverse effects of fluoroquinolones.[6,8] Published case reports and case series have implicated a range of medicines in the development of myoclonus, the most frequently reported being opiates, antidepressants, antipsychotics and antibiotics including beta-lactams and fluoroquinolones.[9] Three published case reports have been found for levofloxacin, all involving older patients.[5]

We assessed the reports in VigiBase for causality and to assess the evidence for the hypotheses that (1) nervous system co-morbidities, and (2) increasing renal impairment leading to higher levofloxacin blood levels and potentially greater CNS penetration, might have contributed to the disproportionate reporting in the elderly.

Reports in VigiBase

More than five thousand reports for levofloxacin under the MedDRA High Level Term (HLT) "Neurological Signs and Symptoms" were identified. These included 45 reports with the MedDRA Preferred Term (PT) myoclonus. More than half (23) were for elderly adults aged 75 years and over, compared with an expected number of 9.5. There were 18 reports for patients aged less than 75 years and in four reports, the age was not stated. All reports entered in VigiBase up to 28 August 2017 for patients aged 75 years and over, in which levofloxacin was a suspect medicine and myoclonus an adverse reaction term, were included in the present analysis.

The reports for patients aged 75 years and older originated from nine countries which were predominantly European. Of the 23 reports, three were excluded. One because the original publication that generated the report did not mention myoclonus, and two because they were duplicates.

The 20 remaining reports included nine men and 11 women with an age range of 78 to 100 years, median 81 years. In comparison, for all reports where age was stated (38) the age range was 15 to 100 years, median 78 years. Twenty patients were men and 18 were women.

Levofloxacin Use

Daily doses ranged from 125 mg to 1000 mg (17 patients). The route of administration was oral for 14 patients and intravenous for three. The duration of levofloxacin use to onset of myoclonus (16 patients) was 1 to 16 days, mean 5.1 days. For 14 patients, onset was within one week.

Levofloxacin was the only suspect medicine related to myoclonus in 14 reports. The symptoms resolved in 11 patients after withdrawal of levofloxacin. These reports are summarised in Table 1. In three of these 11 reports levofloxacin was listed as the only medicine the patient was taking (2, 8, 9) with recurrence on rechallenge in one (2). In report 6, other non-suspect medicines were also discontinued.

Key Case Reports

Key case reports include case report 1 (see table 1), which was published[5] and describes a 78-year-old patient with alcoholism who was treated for pulmonary tuberculosis with isoniazid, ethambutol and rifampicin. After one month he developed peripheral neuropathy attributed to isoniazid. This medicine was discontinued, rifampicin and ethambutol continued and levofloxacin added. After four days he developed myoclonus and other abnormal movements. Levofloxacin was discontinued. He was treated with diazepam and pyridoxine and recovered. He had no further

episodes over the subsequent month, and had normal renal function.

Case report 2 was for an 80-year-old male patient who was treated with levofloxacin for pneumonia and developed myoclonus after nine days. He recovered on stopping levofloxacin and experienced recurrence on rechallenge.

In case report 3, a 79-year-old patient with pneumopathy and epididymitis was treated with levofloxacin and ceftriaxone for 24 hours after which he developed myoclonus and leg cramps. He was found to have sensorimotor deficiency on examination. Levofloxacin was stopped and ceftriaxone continued. He recovered from myoclonus and muscle pain over five days.

Interacting medicines

Drug interactions with levofloxacin were suspected in three reports. In one case, inhibition of clomipramine metabolism by levofloxacin was proposed with resulting serotonin syndrome. In another case, the patient, who had impaired renal function, developed myoclonic jerks after taking memantine for Parkinson's Disease. After two months the patient commenced levofloxacin, the myoclonic jerks worsened and he became confused. The authors of this published report suggested potential competition between levofloxacin and memantine for renal excretion via organic cation transporters (OCTs), as well as chlorphenamine and dextromethorphan contributing to the symptoms.[10] In the third case, the proposed mechanism for an interaction between imipenem and levofloxacin is not recorded but may relate to both fluoroquinolones and beta-lactams predisposing to myoclonus and seizures.

Co-suspect and concomitant medicines

Co-suspect medicines were usually those also reported to cause myoclonus, e.g., mianserin, codeine and ceftriaxone in three reports. However, myoclonus-inducing medicines were also frequently listed as concomitants. Those reported most often were opioid derivatives in four reports and ceftriaxone in three. The complexity of some reports is illustrated by one case describing a patient who developed myoclonus and abnormal movements followed four days later by status epilepticus while taking 11 medicines including levofloxacin, mianserin, codeine and ceftriaxone, all of which may cause myoclonus[9] and predispose to seizures.[11]

Co-reported adverse reactions and co-morbidities

Co-reported adverse reaction terms indicated that some patients had seizures as well as myoclonus. Seizures are rare adverse reactions to levofloxacin[1] and it is possible that some patients were having seizure-related myoclonus without fully developed seizures. Three other patients were described as having encephalopathy (case reports 13, 19, and 20) which levofloxacin may have caused or exacerbated. Other patients had conditions that may have predisposed to levofloxacin-related myoclonus or were an alternative explanation for myoclonus. Two had a background of peripheral or polyneuropathy. Others had cerebral disease, including haemorrhage in two patients, and cortical or subcortical atrophy in three. Metabolic disorders and sepsis may also have impacted on the central nervous system in four patients. Moreover, one patient was under gabapentin treatment which suggests the presence of epilepsy or peripheral neuropathic pain. No predisposing or potentially confounding conditions or co-prescriptions were recorded for reports numbered 2, 8 and 9 in Table 1, and these patients improved on levofloxacin dechallenge. The co-reported adverse reactions and medicines, as well as patient co-morbidities, offer alternative explanations for myoclonus in some cases. However, it is also possible that they predisposed to levofloxacin-related myoclonus given the temporal relationships observed in several case reports with starting and stopping this medicine.

Renal function

Five patients had renal impairment, defined as a creatinine clearance no greater than 50mL/min or specific mention of reduced renal function. Two other reports described renal function as normal at the time of prescription. In the remaining 13 reports renal function was not mentioned, although the dose interval of 48 hours for one of these patients suggested adjustment for renal impairment. It is therefore possible that at least 15 elderly patients with myoclonus did not require levofloxacin dose reduction or that renal function was not measured. Of the five patients with renal impairment, dose adjustments for levofloxacin, as recommended in the US FDA label,[1] appear to have been made for one who was prescribed 125 mg daily. Three were taking 500 or 1000 mg daily, and dose was not recorded for the fifth patient.

Co-reported adverse reactions and co-morbidities

Levofloxacin is the optical S-(-) active isomer of ofloxacin. In two patients with renal impairment ofloxacin levels were 7.4 and 18.4 mcg/mL (therapeutic range 0.5 – 1.5). One had severe renal failure but the levofloxacin dose had been reduced appropriately. Serum ceftriaxone levels were also above therapeutic. This patient recovered when both medicines were stopped. A third patient had a serum levofloxacin level of 9 mcg/mL but a therapeutic range was not reported.

Comparison with levofloxacin/myoclonus reports for patients < 75 years

An overview of the reports for the 18 patients aged 15 to 74 years, median 58 years, supported a causal role for levofloxacin in this age group. In contrast to the older patients, only two had a potentially predisposing cerebral or metabolic disorder and only one had renal impairment. A similarity with the older group was the level of co-prescription with medicines that might cause myoclonus and lower the seizure threshold (8/20 and 6/18). There was one non-steroidal anti-inflammatory drug (NSAID)/levofloxacin interaction in the younger group.

Literature and Labelling

Myoclonus is not listed as an adverse reaction to levofloxacin in the US FDA label or the UK SmPC.[1,2]

The US FDA label for levofloxacin[1] lists convulsions and toxic psychoses as the major CNS reactions reported with fluoroquinolones in clinical trials. A number of other psychiatric and nervous system reactions are listed. These have not been confined to the elderly or those with predisposing conditions. Fluoroquinolones may also increase intracranial pressure and cause CNS stimulation. Peripheral neuropathy has been reported rarely and isolated cases of encephalopathy have been observed since marketing. Myoclonus may therefore be an outcome of other levofloxacin adverse reactions such as seizure activity, encephalopathy and peripheral neuropathy. The elderly are noted to be at increased risk of certain fluoroquinolone-related disorders but these do not include CNS adverse effects. There is a warning that, as with other fluoroquinolones, levofloxacin should be used with caution in patients with a known or suspected CNS disorder that may predispose them to seizures or lower the seizure threshold (e.g., severe cerebral arteriosclerosis, epilepsy) or in the presence of other risk factors that may predispose them to seizures or lower the seizure threshold (e.g., certain drug therapy, renal dysfunction). Recommended dose adjustments for renal failure are provided to avoid levofloxacin accumulation. The UK SmPC for levofloxacin contains similar information.[2]

In 2011, a review was published of psychiatric and neurological adverse reactions attributed to fluoroquinolones, identified through published case reports and case series.[12] Out of the total of 206 adverse reactions, convulsions were most frequently reported. There were six reports of myoclonus, none attributed to levofloxacin. The authors also noted that fluoroquinolone CSF penetration can increase with meningeal inflammation. Levofloxacin is listed as one of the least likely of the fluoroquinolones to cause CNS adverse effects because of low CSF penetration. Although, at the time of the study, ciprofloxacin and levofloxacin were the most widely marketed fluoroquinolones, only 10 adverse reactions attributed to levofloxacin were identified. These included grand mal convulsions (3) and delirium (2).

In keeping with the observations in the VigiBase reports of myoclonus, CNS adverse effects occurred within a few minutes or the first few days of fluoroquinolone treatment and the majority of patients recovered without sequelae when the fluoroquinolone was stopped. Myoclonus occurred with concomitant ofloxacin and pefloxacin in the presence of renal failure in one case report discussed.[12]

Discussion

We describe a case series of patients aged over 75 years who developed myoclonus within days of starting levofloxacin and often recovered when they discontinued this medicine even when there was continuation of co-morbidities or co-prescribed medicines that in themselves could cause myoclonus. It is possible that they had a contributory role in the development of myoclonus. Another potentially contributing factor was renal impairment with little evidence of dose adjustment.

While there was evidence of a causal association between levofloxacin and myoclonus in both age groups, renal impairment and co-morbidities that increase CNS sensitivity were present more often in the elderly group. In contrast, co-prescriptions were potential contributors in both the older and younger age groups.

Although the product labels indicate that increasing age alone does not increase the risk of levofloxacin-related CNS adverse effects these are more likely to occur in the elderly as renal function diminishes with age, accelerated by some age-related clinical conditions. This decline may not always be detected if serum creatinine is low due to decreased muscle mass. Thus, accurate measurement of renal function and dose adjustment to avoid accumulation of levofloxacin is essential. However, there is discussion about the most appropriate dose adjustment regime to maintain efficacy as well as reduce toxicity.[13,14] The level of adjustment is based on the initial recommended dose for the presenting infection and the degree of renal impairment. However, the emphasis on decreasing the dose or increasing the dose interval varies, for example, between the US FDA label[1] and the UK SmPC.[2]

CNS morbidities predisposing to myoclonus also increase with age as do co-prescriptions. However, co-prescribing of medicines that might induce myoclonus was an issue for all age groups. Many of these medicines also decrease the seizure threshold.[9,11] and several patients had seizures in this case series. For some patients complex treatment with several medicines, including

multiple antibiotics, all of which can lead to myoclonus and seizures, is unavoidable. However, the reports support product label advice to avoid these combinations whenever possible.

A recent US FDA Black Box Warning for fluoroquinolones advises restriction of the use of these antibiotics in infections for which a choice of antibiotics is available, because of serious reactions including CNS effects.[1] Dose adjustment in renal failure, careful review of co-prescriptions and monitoring of patients with predisposing CNS conditions should also reduce the possibility of myoclonus and seizures.

Conclusion

Of the 20 VigiBase reports of levofloxacin and myoclonus in the elderly, 11 described a temporal relationship with levofloxacin use that supported causality. In three of these reports there were no medicines or co-morbidities that may have contributed or been alternative explanations. Renal impairment, and CNS conditions that may predispose to myoclonus were more prevalent in the reports for patients over 75 years. In contrast co-prescription of medicines that may cause myoclonus and lower the seizure threshold was prominent in all age groups and the reports are a reminder to identify avoidable combinations.

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Table 1. Characteristics of reports of recovery on levofloxacin dechallenge.

Case	Age/ Sex	Indication	Daily dose	Treatment duration	Route	Time to onset	Other Suspected (S), Concomitant (C) or Interacting (I) Medications	ADRs co-reported with myoclonus	Outcome and Additional information
1	78/M	Pulmonary tuberculosis	500 mg	-	-	4 days	Ethambutol (C), Rifampicin (C)	Chorea	Recovery on dechallenge. Normal renal function. Isoniazid-related peripheral neuropathy.
2	80/M	Pneumonia	750 mg	9 day (s)	-	9 days	-	-	Recovery on dechallenge and positive rechallenge
3	79/M	Pneumopathy, Epididymitis	1000 mg 500 mg	1 day (s) 1 day (s)	Oral	1 day	Bisoprolol (C), Ceftriaxone (C), Omeprazole (C), Potassium (C)	Myalgia	Recovery on levofloxacin dechallenge, ceftriaxone continued. Sensorimotor deficit, Cr Cl Clearance 34mL/min one month prior to levofloxacin, normal on starting.
4	81/M	Pneumopathy	500mg	5 day (s)	Oral	5 days	Acetylsalicylic acid (C), Alfuzosin (C), Amlodipine (C), Atorvastatin (C), Bisoprolol (C), Clopidogrel (C), Esomeprazole (C), Furosemide (C), Glyceryl trinitrate (C), Paracetamol (C)	-	Recovery on dechallenge. Treated with clonazepam and levetiracetam. Myoclonus considered epileptic. Cortico-sub-cortical atrophy.
5	78/M	Prostatitis	500 mg	3 day (s)	Oral	3 days	Bicalutamide (C), donepezil (C), memantine (C)	Coma	Recovery of myoclonus on dechallenge. Dementia. Died of pneumopathy.
6	78/F	Urinary tract infection	1000 mg	7 day (s)	Oral	7 days	Amoxicillin/clavulanic acid (C), Furosemide (C), Hydrocortisone (C), Omeprazole (C), Paracetamol (C), Spironolactone (C), Zolpidem (C)	Renal failure aggravated	Recovery myoclonus & aggravated renal failure on dechallenge, levofloxacin and concomitants. Treated with clonazepam. Cardiac failure likely cause of aggravated renal failure.
7	82/F	Pneumopathy	1000 mg	7 day (s)	Oral	6 days	Aspirin (C), urapidil (C), nadolol (C), hydrochlorothiazide (C)	Encephalopathy (multifocal, multifactorial), Cheyne-Stokes respiration	Recovery on dechallenge. Parkinson's Disease, severe hypernatremia. Cortical and subcortical atrophy, sepsis, lactic acidosis.
8	86/F	Bronchitis	500 mg	30 day (s)	Oral	7 days	-	Visual hallucination	Recovery on dechallenge. Possible medication error, not confirmed.
9	78/F	Respiratory infection	500 mg	5 day (s)	Oral	4 days	-	-	Recovery on dechallenge.
10	79/M	Pneumopathy	1000 mg	6 day (s)	Intra-venous	4 days	Clavulanic acid (C), Ticarcillin (C)	Encephalopathy	Recovery on dechallenge. Preceding haemorrhagic stroke possible. Ofloxacin serum level 18.4 mcg/mL. EEG slow, no epileptic elements.
11	89/F	-	-	16 day (s)	Oral	16 days	Amiodarone (C), Digoxin (C), Fluindione (C), Isosorbide Dinitrate (C), Molsidomine (C), frusemide (C), lansoprazole (C), ambroxol (C), metoclopramide (C)	Encephalopathy (Confusion, agitation)	Recovery on dechallenge Cr Cl 30mL/min. Meningeal haemorrhage on lumbar puncture but not on scan. EEG very slow suggesting encephalopathy of metabolic origin. INR 10.8, Levofloxacin serum level 9 mcg/mL.

Methotrexate – Incorrect drug administration rate

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Methotrexate is a folic acid antagonist used in the treatment of rheumatoid arthritis and severe psoriasis when the patient has been unresponsive to other, conventional therapies.[1,2] It is also used to induce regression in neoplastic conditions such as acute leukaemia, non-Hodgkin's lymphoma, soft-tissue and osteogenic sarcomas, and solid tumours such as breast, lung, head and neck, bladder, cervix, ovaries, and testicles carcinoma. In the treatment of rheumatoid arthritis and psoriasis, methotrexate is given as a weekly dose. This dose can be divided into three doses to be taken within 24 hours, at 12-hour intervals (applicable for the tablet formulation). In cancer treatment, single doses of methotrexate are given on not more than five consecutive days, followed by a rest period of at least two weeks between treatments.

In VigiBase, there are 24 cases reporting incorrect drug administration rate for methotrexate between 2009 and January 2018. Thirteen cases are from France, three from Bulgaria, three from USA, and one each from Denmark, Germany, Spain, Switzerland and UK. The patient age ranged from 3 to 92 years, with a median age of 63 years, based on the 21 reports where age was provided. Men accounted for 15 and women for 9 reports. The indications for treatment were reported as psoriasis in three cases, rheumatoid arthritis in three cases, various cancers in three cases (acute lymphocytic leukaemia, B cell lymphoma, cerebral lymphoma), bullous pemphigoid in one case and asthma in another case. In the remaining 13 cases, the indication was unspecified. Methotrexate was administered intravenously in five cases and orally in 19 cases.

In the cases where oral methotrexate was prescribed, the patients had taken it daily instead of weekly. In one case, a prescription error was reported. However, in most cases it appears that the patient did not understand that methotrexate was to be taken weekly and not daily. In addition to errors in administration, other reactions were reported. The five most reported reactions included mouth ulceration (4), thrombocytopenia (4), gastritis (4), pancytopenia (3) and pharyngitis (3). The outcome was recovered in 15 cases, not recovered in one case and unknown in another case. In the remaining two cases, the patient died.

Both the Summary of Product Characteristics (SmPC) and the Patient Information Leaflet (PIL) state that methotrexate is to be taken weekly.[1,3] However, these reports show that the patient took it daily instead, with significant adverse effects. The dosing instructions can be particularly confusing in the cases where the weekly dose is divided into three doses to be taken within 24 hours, with a 12-hour gap between each dose. Based on the reports in VigiBase, it appears that clearer instructions both in the SPC and by the prescriber are necessary, and that health care professionals should verify that the patient has understood how the medication needs to be taken.

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Omalizumab and anaphylactic shock in females

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Summary

Omalizumab is an anti-IgE antibody indicated for moderate to severe persistent allergic asthma and chronic idiopathic urticaria resistant to H1 antihistamine treatment.

One of the adverse reactions of omalizumab is anaphylaxis, and in particular anaphylactic shock, which occurs suddenly and may cause death. Anaphylaxis is labelled in the US Summary of Product Characteristics (SPCs) and in the EU SPCs.

A screening conducted in October 2017 at the Uppsala Monitoring Centre (UMC), utilizing VigiBase, the WHO global database of individual case safety reports (ICSRs), showed a large gender asymmetry of cases of anaphylactic shock among users of omalizumab (91 reports vs 61 expected for females; and 14 reports vs 32 expected for males)[a].

All reports of "omalizumab – anaphylactic shock" present in VigiBase have been reviewed to determine the imputability on the basis of the data contained in the reports, with or without narrative. At the end of the imputability process, nine reports for males and 40 for females were judged as "possible" or "probable", with a M/F ratio of 1:4.4 instead of 1:6.5. Therefore, the difference between males and females in the number of anaphylactic shock remains large even after the analysis of the imputability.

Recently, one in vivo study using mice suggested that females are more prone to anaphylactic shock, providing a possible mechanistic explanation. The presence of an animal model that suggests a gender difference in the sensitivity to anaphylaxis can be regarded as supportive of the biological plausibility of the signal. However, it is also important to consider that the process of signal detection requires that a significant number of subgroups are routinely screened for a large number of drugs and suspected reactions. This process inevitably carries a risk of highlighting anomalous findings only by chance (false positive signals).

In conclusion, the signal "anaphylactic shock - omalizumab - female gender", even though potentially attributable to the role of chance, should be taken into account and the consistency of the signal over time should be assessed.

Introduction

Anaphylactic shock is a severe clinical manifestation that occurs suddenly and may cause death. It typically causes more than one of the following: an itchy rash, throat or tongue swelling, shortness of breath, vomiting, lightheadedness, low blood pressure and loss of consciousness. These symptoms occur typically over minutes to hours. Many drugs can induce anaphylactic shock, either with an immunological or an "idiosyncratic" (not immunological) mechanism.

Omalizumab is a recombinant humanized anti-IgE antibody that inhibits the activity of IgE, thus preventing the binding of IgE to high-affinity IgE receptor (FcεRI) on the surface of mast cells and basophils. The reductions in surface bound IgE on FcεRI bearing cells limits the release of mediators of the allergic response.[1]

Omalizumab is indicated as add-on therapy to improve asthma control in adult and adolescent patients (12 years of age and above) with severe persistent allergic asthma. The dose applied for is 150 – 375 mg subcutaneously, every two or four weeks, depending on the baseline serum total IgE level, measured before the start of the treatment, and body weight. The drug has been approved in the EU since October 2005.[2]

Since 2014 in the EU, omalizumab is also indicated as add-on therapy for the treatment of chronic spontaneous urticaria in adult and adolescent patients (12 years and above) with inadequate response to H1 antihistamine treatment.[3]

A suspected signal (combination of omalizumab and anaphylactic shock in females) arose from a screening conducted in October 2017 at the Uppsala Monitoring Centre (UMC), when the analyses focused on various drug-ADR combinations. Different covariates such as age, BMI, gender and country were analyzed. The aim was to detect potential signals for subgroups of patients (e.g. underweight/overweight for the BMI covariate) and to characterize possible risk factors for adverse drug reactions. The combination omalizumab and anaphylactic shock stood out for females when compared to the overall reporting rate of the female subgroup.

Literature and Labelling

Anaphylaxis is labelled in the US Summary of Product Characteristics (SPCs) with a boxed warning that suggests measures to cope with this risk.[4] In the EU SPCs "Anaphylaxis" is mentioned. The EU SPC evaluates, on the basis of an exposure amounting to 566,923 patients/year, a reporting rate of 0.2%. However, there is no specific mention

[a] Clarified following company response to signal

that females could be at an increased risk for anaphylactic shock.[1]

Several studies are present in the literature, indicating a higher incidence of anaphylaxis in the female gender in association with food,[5] drugs[6-8] and contrast media.[9] On the other hand, in another study, males were more implicated in anaphylaxis.[10] Recently, an in vivo study using mice, suggested that females are more prone to anaphylactic shock, providing a possible mechanistic explanation. The greater severity of anaphylaxis in female mice was eliminated after pretreatment with an estrogen receptor antagonist or ovariectomy, but restored after administration of estradiol in ovariectomized mice, demonstrating that the sex-specific differences were attributable to the female steroid estradiol.[11]

Results

The case series consisted of 91 reports vs 61 expected for females and 14 vs 32 expected for males from VigiBase, the WHO global database of individual case safety reports (ICSRs).[b] All cases have been reviewed to determine the imputability on the basis of the data contained in the reports, with or without narrative.

Among the cases which report the indication of use, the majority were being treated for asthma, the rest mainly for chronic idiopathic urticaria, and a few for mastocytosis.

At the end of the imputability process, cases judged "possible" or "probable" came to nine for males and 40 for females (Table 1), with a M/F ratio of 1:4.4 instead of 1:6.5 (still a fairly high ratio). Three cases in males and 40 in females were judged "not assessable", because of lack of data to carry out an imputability decision, but also because of data erased from reports for reasons of privacy. Two cases concerning males and 11 concerning females resulted in "unrelated" or "doubtful". Cases with anaphylactic shock that occurred more than 24 hours after the omalizumab administration were considered as "unrelated".

Table 1. Evaluation of the reports in VigiBase of anaphylactic shock in association with omalizumab.

Imputability	Females	Males	Total
Probable	27	7	34
Possible	13	2	15
Doubtful	3	0	3
Unrelated	8	2	10
Not assessable	40	3	43
Total	91	14	105

We have compared the male reports for this drug-ADR combination and the disease status: they were very similar to the female subgroup of interest (the indication for omalizumab being in both severe asthma). We also did not find any alternative reason to explain why the female subgroup stood out in this drug-ADR combination.

Discussion and Conclusion

Anaphylactic shock is a very serious clinical condition, with a high risk of death, that is unlikely to be confounded with other adverse reactions. As omalizumab is administered subcutaneously, an anaphylactic reaction with shock takes place in a narrow time window, from few minutes to some hours.

After the review of the imputability of all cases, the difference between males and females in the number of anaphylactic shock is still large.

In the literature we did not find any studies that investigated the association between the use of omalizumab and gender differences in the occurrence of anaphylaxis. Two studies showed a greater frequency of anaphylaxis for females among users of N-acetylcysteine[12] and of neuromuscular blocking drugs.[13]

Recently, a study on mice has shown an increase in the severity of anaphylaxis associated with the estrogens.[11] The authors deemed that the anaphylactic response was more pronounced in female than in male mice.

The presence of an animal model that suggests a gender difference in the sensitivity to anaphylaxis can be regarded as supportive of the biological plausibility of the signal. However, it is also important to consider that, as clearly indicated by UMC colleagues, the process of signal detection requires that a significant number of subgroups are routinely screened for a large number of drugs and suspected reactions. This process inevitably carries a risk of highlighting anomalous findings only by chance (false positive signals).

In conclusion, in my opinion the possible signal "anaphylactic shock - omalizumab - female gender", even though potentially attributable to the role of chance, should be taken into account.

It would be useful to assess the consistency of the signal over time and, if confirmed, to carry out ad hoc observational studies.

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Xolair® (omalizumab) Novartis comment on draft Signal from UMC – WHO Collaborating Centre for International Drug Monitoring

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Background

The signal report by the Uppsala Monitoring Centre (UMC) investigated the number of Individual Case Safety Reports (ICSRs) of anaphylactic shock reported for female and male omalizumab users. They observed a gender asymmetry with 4.4-6.5 times more female than male ICSRs which was discussed in the context of published animal and human data providing potential explanations for a higher anaphylaxis risk in women. The signal could not be validated with available data. UMC finally concluded that, the possible signal "anaphylactic shock - omalizumab - female gender" though potentially attributable to the role of chance, should be taken into account. It would be useful to assess the consistency of the signal over time.

Evaluation by Novartis

Anaphylaxis including anaphylactic shock is a known and well-characterized identified risk for omalizumab by: 1) a large clinical trial database (>15,500 patients) 2) post-marketing exposure (>950,000 PTY) and two specific observational studies - XPAND (Lieberman 2016) and XPAND 2 (Lieberman 2017).

Gender asymmetry in reporting of anaphylaxis with Xolair is not a new finding. In the XPAND study (a case controlled study) it was observed that there were more females (N=27) [90%] who experienced anaphylaxis than male (N=3). A similar finding was observed in the XPAND 2 study Male/Female (M/F) ratio: 1:5.25 (16% vs. 84%). A preponderance of female anaphylaxis case subjects has also been reported previously from omalizumab anaphylaxis case data in the FDA adverse event reporting system (AERS) from 2003-2006 (82% female, Limb 2007) and 2007-2008 (76% female, Lin 2009).

The analysis done by UMC is based on the M/F ratio of absolute number of ICSRs in Vigibase and does not consider the back ground population or the extent of exposure by M/F. A M/F ratio based on the absolute number of anaphylaxis reports for omalizumab ignoring any gender difference in the treated population is only an appropriate measure of risk ratio if,

- Overall number of omalizumab reports for females and males is the same
- There is no gender-specific differential reporting

However, the M/F ratio in omalizumab prescribing data (PSUR with cut-off date 31 Dec 2017) is approximately 1:2.1 (32% male vs. 67% female; gender unknown in 1%). Thus, based on prescriptions, approximately two fold more reports are expected for females (if nondifferential reporting). We also see the same pattern in all adverse events reported in Novartis Safety Database with an M/F ratio of 1:2.3 (18,866 males vs 43,872 females).

Novartis safety database

Cumulatively until 31 Dec 2017, the Novartis Safety database included 191 cases of MedDRA PT "Anaphylactic shock'. Gender was reported in 181 cases (153 female and 28 male). The reported indication was asthma in 60%, CSU in 18% and other indications in 22% of the reports.

The M/F ratio of anaphylactic shock cases was 1:5.5 (28/153) which is in line with UMC's observation. To take into account that omalizumab is prescribed two times more often two females (67%) than to males (32%), Novartis has calculated the reporting rate (RR) of anaphylactic shock by gender based on post-marketing exposure (Table 2-1). Based on the RR, the M/F ratio reduced to 1:2.6 (0.09/0.24).

Table 2-1 Reporting rate (RR) of anaphylactic shock by gender

Gender	Number of cases of Anaphylactic shock	Post marketing exposure in patient treatment years (PTY)*	RR per 1000 PTY
Male	28	314469	0.09
Female	153	650357	0.24

*Source: PSUR (01 Jan 2017-31 Dec 2017)

Literature

Gonzalez-Perez et al. 2010 investigated the risk of anaphylaxis in large cohorts of patients with and without asthma based on the UK THIN (The Health Improvement Network) database. They found women with severe asthma are at approximately 2-fold higher risk of anaphylaxis than men with severe asthma (Incidence rate ratio: 1.91; 95% CI: 1.18-3.15). This study also showed that the risk difference between male and female was higher in the age group of 10-59 years. The risk difference was reduced extensively in the age group 60 years and beyond.

A review article (M Tejedor-Alonso 2015) looked into the epidemiology of anaphylaxis based on data published in last 10 years. Several publications who examined a representative sample from primary care in UK, found that the frequency of anaphylaxis is greater in males until 10-15 year of age but women experienced more episodes after the age of 15 years.

The in vivo study (Hox V et al, 2015) demonstrated sex-dependent differences in a Passive Systemic Anaphylaxis (PSA) mouse model, along with role that estradiol may play in the severity and/or duration of anaphylaxis. The investigators have identified a possible mechanism of action, an estradiol-dependent upregulation of eNOS (endothelial nitric oxide synthase) and nitric oxide production affecting the severity and/or duration of anaphylaxis in female versus male mice.

Discussion and Conclusion

The risk of anaphylaxis including anaphylactic shock is an identified risk for omalizumab and well characterized. The current risk minimization measures in the labeling documents are adequate to manage the risk.

Novartis acknowledges the higher reporting of anaphylactic shock in females compared to male in the terms of absolute number of cases (M/F = 1:5.5 based on Novartis safety database without immutability). However, comparing RRs by exposure, the M/F ratio became 1:2.6. This ratio is consistent with the higher anaphylaxis risk in women with severe asthma. (Gonzalez-Perez 2010)

and possible mechanistic evidence is also available (Hox V 2015).

In conclusion, an excess risk of anaphylaxis attributable to omalizumab in females, i.e. the possible signal of "anaphylactic shock - omalizumab - female gender", could not be confirmed with the available data.

Novartis will continue to monitor this safety observation over time through routine signal detection process.

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CAVEAT DOCUMENT

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs).
Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

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 Programme for International Drug Monitoring. The information is stored in VigiBase, the WHO global database of individual case safety reports (ICSRs). It is important to understand the limitations and qualifications that apply to this information and its use.

Tentative and variable nature of the data

Uncertainty: 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 is the cause of an event, rather than, for example, underlying illness or other concomitant medication.

Variability of source: Reports submitted to national centres come from both regulated and voluntary sources. Practice varies: some national centres accept reports only from medical practitioners; others from a broader range of reporters, including patients, some include reports from pharmaceutical companies.

Contingent influences: 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 adverse effects and other factors.

No prevalence data: No information is provided on the number of patients exposed to the product, and only a small part of the reactions occurring are reported.

Time to VigiBase: Some national centres make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of an ICSR by a national centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from that obtained directly from national centres.

For these reasons, interpretations of adverse effect data, and particularly those based on comparisons between medicinal products, may be misleading. The data comes from a variety of sources and the likelihood of a causal relationship varies across reports. Any use of VigiBase data must take these significant variables into account.

Prohibited 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 VigiBase must include a statement:

(i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information

(ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases

(iii) affirming that the information does not represent the opinion of the UMC or 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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Recommendations from the 41st 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 each other, WHO and WHO Collaborating Centres (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 future of PV. Recommendations are made by delegates through group work. The forty first annual meeting of representatives of NPCs participating in the WHO PIDM was held from 6 to 8 November 2018, in Geneva, Switzerland. The meeting included eight working groups that discussed various issues in PV. The summary of discussions and the recommendations are described in this article

Working group 1. Regional platforms: when and how they can be of benefit

The aim of this workshop was to discuss how and when countries can benefit from a regional platform. During discussions, the working group stressed the value of information sharing and training that a regional platform can bring. Additionally, the platforms form a network for more personal interactions. Potential challenges such as the use of different languages, bureaucracy and politics, and technological problems were highlighted. Group members stated that the purpose of a regional platform needs to be clear to all, and people should be able to see the common benefits. In developing such a platform, it was suggested to start small by offering a few services and gradually build on that to grow. Key features are to be flexible and to take into account peoples' needs.

Recommendations

To WHO and WHO Collaborating Centres:

- Map out all current collaborations within a regional platform and identify the successful collaborations.
- Give guidance on principles of collaboration and provide technical assistance.

To National pharmacovigilance centres:

- Show willingness and commitment in their regions.
- Identify priorities that may differ between regions.

Working group 2. Educational tools: what and when

This working group discussed what the optimal contents and format of an educational toolkit should be. Members suggested that existing educational materials should be considered before developing new tools. Common elements between different groups of stakeholders at different levels of required expertise should be considered. Suggestions were made as to the topics to be covered by educational tools at different levels (pharmacovigilance staff, undergraduates, health-care professionals, patients). The group recommended starting with train-the-trainers sessions, to build a bigger pool of trainers so that educational tools are used more widely.

Recommendations

To WHO and WHO Collaborating Centres:

- WHO and WHO Collaborating Centres should develop training materials, host workshops and develop online training tools in different languages.
- WHO should provide recommendations to national pharmacovigilance centres on developing educational strategies for different target groups.

To National pharmacovigilance centres:

- Before starting a new educational tool, make an inventory of existing material

- A set of core educational materials should be in each toolkit, but each kit should be geared to the needs of a specific group of persons to be trained.
- Start with train the trainer workshops so that the workload for trainers is distributed.
- Nonconventional approaches could include:
  - incorporating pharmacovigilance issues into Public Health campaigns
  - using crisis situations as opportunities to educate
  - arranging for an exhibition about vaccines
  - running campaigns in local languages
  - holding a special reporting day
  - including pharmacy contact information in the dispensing package
  - participating in social media groups.

Working group 3. Improving communication

The working group discussed integration of PV and communication processes by examining the management and governance of communication, and the processes and mechanisms required to learn about the information needed by different audiences. The group reviewed the tasks of the pharmacovigilance communication team and discussed what qualifications the staff members would need. Both internal and external communication are important.

Recommendations

To National pharmacovigilance centres:

- Pharmacovigilance communication should be part of the organizational strategy and long-term planning.
- The strategic plan for the National PV Centre should contain communication training for staff.
- A database of experts or opinion leaders with their contact details should be created to obtain rapid support, help and feedback for communication.
- Stakeholders should be consulted on their preferred modes of communication.
- The present situation of the National PV Centre and communications (structure, staff, finances, core and support processes, risks) should be analysed.
- When forming a communication strategy, organisations should consider what exists, decide what is needed, and form a plan with timelines and processes.
- Local focus groups are a good way to learn about people's views for communication.
- Communication should not be only responsive; it must be proactive.

Working group 4. Strategies for improving the quality of information in Individual Case Safety Reports (ICSR)

The objectives of the working group included reviewing current practices and reporting forms and identifying best practices for improving quality of reports. Good-quality reporting is needed to improve data analysis, causality assessment and signal detection. There is a need to adopt practices that: reduce time spent on follow-up of incomplete reports; and improve the quality of reports received from marketing authorization holders. Problems with reporting forms (both paper-based and online) were noted. These include complexity, lack of consistency and the use of different reporting forms for different programmes.

Recommendations

To WHO and WHO Collaborating Centres:

- Develop online training modules for health-care professionals on why completeness of reports is important.
- Design an online reporting form that has the same interface for healthcare providers and patients. The online reporting system should provide automatic feedback on incomplete fields.
- Provide a standardised reporting form.

To National Pharmacovigilance Centres:

- Retest online reporting platforms before final introduction.
- Institute a quality management system to ensure that only qualified staff carry out data entry and coding.
- Provide information to users (health-care professionals and patients) on how to complete important fields by:

- putting explanatory videos on YouTube
- including a tutorial on completeness as part of an online reporting tool.

- Train health-care professionals on the importance of completeness of ICSRs (with UMC).
- Institute a quality management system to ensure that only qualified staff carry out data entry and coding.
- Adopt internal reviews on an ongoing basis at the pharmacovigilance centres for quality reports.

Working group 5. Rational use of drugs

The working group examined the varied reasons for the irrational use of drugs, including self-medication, poor communication, inappropriate training, lack of diagnostic procedures, patient pressure, promotion of drugs by manufacturers, ineffective supply, drug addiction and substitution. The consequences of irrational use include polypharmacy, multi-drug prescribing, antibiotic overuse, microbial resistance, a lack of confidence in the health-care system by the public and harm to the environment.

Recommendations

To WHO and WHO Collaborating Centres:

- More regional workshops to promote rational use of medicines and information exchange should be organized and supported.
- Regional guidelines on rational drug use should be developed and implemented.
- Information on antimicrobial resistance should be promoted, collected and shared.
- Data on antimicrobial use should be collected and aggregated at regional level.
- WHO should coordinate activities on the rational use of drugs and antimicrobial resistance.
- Data, information and guidelines on rational drug use should be disseminated.

To National pharmacovigilance centres:

- Extend the scope of activities to include promotion of rational use.
- Collate and publish information on antimicrobial resistance in the region.
- Promote guidelines for rational use of medicines.
- Lead an advocacy visit to ministries of health and professional bodies relating to policies and guidelines.
- Promote educational activities encouraging the rational use of medicines, with warnings and consequences of inadequate drug use.
- Link pharmacovigilance data with drug formularies.

Working group 6. Monitoring medicines safety in special populations

The working group defined special characteristics of pharmacovigilance in the paediatric population, the elderly, during pregnancy, and in patients with concomitant diseases such renal and hepatic impairment. They noted that many medicines are not currently available in formulations suitable for administration to children. Elderly persons are exposed to polypharmacy because of comorbidities. In addition, lack of compliance occurs with a higher frequency or is more serious in these populations.

Recommendations

To WHO, WHO Collaborating Centres and National Pharmacovigilance Centres:

- Proposed methodologies for increasing reporting and detection of adverse drug reactions (ADRs) in special populations include:
  - educational programmes and materials for physicians, caregivers of children and geriatrics
  - development of specific tools for data-mining, subset analysis, etc
  - training packages for regulators and health-care providers
  - drug utilization reviews
  - communication
  - establishment of registries
  - collaboration with special interest groups (e.g. paediatricians)

Working group 7. Reporting and preventing medication errors

The working group discussion covered the preventability of ADRs resulting from medication errors.

Existing definitions, terminologies and methodologies for managing medication errors (ME) were also discussed, with differences noted across the US, EU and other countries. There is variation in the way reports may be managed at a regional/local level; national responsibilities and cultural/clinical practices should be considered in the interpretation and management of cases.

Given the necessity for ME reporting, the concept of a 'no blame' culture was considered an important aspect of ME reporting overall, together with appropriate protection of the confidentiality of sources. However, it was also acknowledged that in some cases/countries, where an issue of negligence was reported/observed, these could be legal/court proceedings.

The practical regulatory activities to minimise the risk of ME, including proactive planning in the context of regulatory assessments, naming, labelling and product packaging issues, as well as the need to adapt risk management plans, to the local setting were also discussed.

Recommendations

To WHO and WHO Collaborating Centres
- Undertake a survey to identify practices and frameworks in place for ME reporting in participating countries.
- Build and strengthen capacity for national centres to manage ME reports through technical support, guidance and training.
- Provide a link to other relevant initiatives, including the Global Challenge on ME and International Medication Safety Network (IMSN) activities.
- Develop training materials and guidance.
- Provide/contribute to training activities, including assessment of cases, where needed/appropriate.
- Highlight/publish experience to alert others and to show successes.

To national pharmacovigilance centres:
- Identify relevant, national organisations (e.g. risk management teams at hospital level, poison control centres, medication safety groups etc.) and establish processes for interaction and follow up on ME related matters, as appropriate.
- Undertake training nationally for health-care professionals.
- Promote and facilitate public awareness.
- Promote a 'no blame' culture to support and encourage reporting of ME, protecting the confidentiality of reporters, as appropriate.
- Promote the use of risk reduction strategies as far as possible, including e-prescribing (where feasible), use of prescribing alerts, use of bar codes for products etc.
- Support provision of resources to facilitate and manage reports of ME in a timely manner.
- Consider implementation of the P-method[3] to detect and manage ME, where appropriate.

Working group 8. Reporting quality problems

The working group discussed collaboration between pharmacovigilance centres on post-marketing surveillance and drug safety.

Recommendations

To WHO and WHO Collaborating Centres:
- Ensure that the details of national focal points for pharmacovigilance and for substandard and falsified medical products are shared with countries in order to strengthen collaboration and cooperation at national level.
- Report progress and good practices to the 42nd Annual Meeting of National Pharmacovigilance Centres.

To National Pharmacovigilance Centres:
- Develop campaigns to increase awareness of substandard products.
- Develop and implement an advocacy and awareness campaign on pharmacovigilance and medicine quality reporting systems targeting health-care professionals in 2019; and measure its effectiveness post-campaign.

[3] A method used to systematically detect medication errors in ICSRs sent to pharmacovigilance centres. It can be applied to any reported adverse event once a reasonable link between the event and the suspected drug has been validated by causality assessment.

- Develop and implement processes and procedures to ensure effective, regular and timely communication and collaboration between reporting systems of national pharmacovigilance and medicine quality departments.