

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,

EMP-HIS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pvsupport@who.int

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 the WHO global database of individual case safety reports, VigiBase.

This newsletter includes a feature article with the recommendations from the 40th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

Contents

Regulatory matters

Safety of medicines

Signal

Feature

© World Health Organization 2018

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: “This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition”.

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization.

Suggested citation. WHO Pharmaceuticals Newsletter No.1, 2018: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

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

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Printed in Switzerland

Regulatory Matters

Aripiprazole.....	5
Cladribine	5
Clozapine.....	5
Dengvaxia®.....	5
Edoxaban	6
Eluxadoline	6
Epoetins	6
Fingolimod.....	7
Flucloxacillin and concomitant paracetamol	7
Gadolinium-based contrast agents (GBCAs)	8
Idelalisib.....	8
Iodine-containing contrast agents.....	9
Ipilimumab	9
Lenvatinib.....	9
Long-acting beta agonists (LABAs) and inhaled corticosteroids (ICS).....	9
Opioid cough and cold medicines (prescription)	10
Paracetamol (modified-release) containing products.....	10
Proton Pump Inhibitors (PPIs)	10
Sedative and anaesthetic drugs (other than benzodiazepines and barbiturates).....	11
Tacrolimus products (oral)	11
Teriparatide	11

Safety of Medicines

Antiepileptic drugs	13
Benzodiazepines and barbiturates.....	13
Chlorhexidine	13
Ibuprofen	13
Interferon beta-1a	14
Quinine	14
Radium-223 dichloride in combination with abiraterone and prednisone/prednisolone.....	14
Rolapitant.....	15
SGLT2 inhibitor	15

Signal

Ciprofloxacin, enalapril and acute kidney injury: strengthening of a drug interaction signal 16

Ivermectin and serious neurological events 21

Feature

Recommendations from the 40th Annual Meeting of Representatives of the National Pharmacovigilance Centres Participating in the WHO Programme for International Drug Monitoring 28

Aripiprazole

Risk of impulse-control disorder

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for aripiprazole (Abilify®) has been updated to include the risk of impulse-control disorder as a precaution.

Aripiprazole is indicated for schizophrenia, improvement of manic symptoms in patients with bipolar disorder, depression, depressed state (within certain limits) and irritability accompanying childhood autism spectrum disorder.

Four cases associated with impulse-control disorder have been reported in Japan. The causal relationship was not evaluated. The company core datasheet (CCDS) has also been updated. In addition, the US Food and Drug Administration (FDA) and the Australian Therapeutic Goods Administration (TGA) have also updated package inserts to include the risk of impulse-control disorder.

Reference:

Revision of Precautions, MHLW/PMDA, 11 January 2018 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletters No.2, 2017: Risk of impulse control disorders, No.3, 2016: Risk of impulse-control problems in the USA and No.6, 2015: Risk of certain impulse control behaviours in Canada)

Cladribine

Risk of progressive multifocal encephalopathy (PML)

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has updated the product information for cladribine preparations (Litak®,

Leustat®) to include the risk of progressive multifocal encephalopathy (PML) as a potential adverse drug reaction.

Cladribine is indicated for hairy cell leukaemia and B-cell chronic lymphocytic leukaemia.

As of March 2017, three confirmed reports of PML (including at least one fatal case) have been reported worldwide in patients taking cladribine for various haematological conditions. None of these reports originated from the United Kingdom.

Health-care professionals are advised to consider PML in the differential diagnosis for patients with new or worsening neurological signs or symptoms, even several years after treatment with cladribine. A letter has been sent to haematologists and oncologists about this risk.

Reference:

Drug Safety Update, MHRA, Volume 11, issue 5: 2, December 2017 (www.gov.uk/mhra)

Spain. La Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) has recommended that health-care professionals perform a differential diagnosis in patients who present new neurological symptoms or worsening of the pre-existing symptoms while using cladribine, and suspend use in those with suspected PML.

Cladribine is indicated for the treatment of hairy cell leukaemia (PCL) (Leustatin® and Litak®) and chronic lymphocytic leukaemia (Leustatin®).

Several cases of PML associated with the use of cladribine have been reported in Europe. Of these, one had a fatal outcome with a clear diagnosis and no identified confounding factors.

In the cases reported, the diagnosis of PML was made

from six months to several years after the end of treatment with cladribine. Additionally, there is a clear biological plausibility since prolonged lymphopenia induced by cladribine is a potential risk factor for PML.

Reference:

Información para profesionales sanitarios, AEMPS, 1 December 2017, Spain (www.aemps.gob.es)

Clozapine

Risk of pleurisy

Japan. The MHLW and the PMDA have announced that the package insert for clozapine (Clozaril®) has been updated to include the risk of pleurisy as a clinically significant adverse reaction.

Clozapine is indicated for treatment-resistant schizophrenia.

Six cases associated with pleurisy have been reported in Japan. Of these, a causal relationship could not be excluded in one case. The company core datasheet (CCDS) has also been updated.

Reference:

Revision of Precautions, MHLW/PMDA, 28 November 2017 (www.pmda.go.jp/english/)

Dengvaxia®

Risk in individuals with no prior experience of dengue infection

Singapore. The Health Sciences Authority (HSA) has strengthened warnings and recommendations in the prescribing information for Dengvaxia® about the increased risk of developing clinically severe dengue in individuals not previously infected by dengue.

The package insert provides advice on assessing individuals for a history of previous dengue infection before vaccination, and states that vaccination is not recommended for individuals who have not been previously infected with dengue.

Dengvaxia® is used for the prevention of dengue infection caused by dengue virus (serotypes 1, 2, 3 and 4) in individuals aged between 12 and 45 years. Currently in Singapore, dengue vaccination is not part of the national immunisation programme.

Results from clinical and long-term safety studies by the manufacturer confirmed that there is a postulated risk of a higher incidence of severe dengue following vaccination in individuals who have not been previously infected by dengue.

All health-care professionals have been issued advice on these findings and were informed of the recommendation not to vaccinate individuals who have no history of a previous dengue infection. The HSA will monitor the vaccine closely to ensure continued safety and efficacy.

Reference:

HSA Updates, HSA, 1 and 8 December 2017 (<http://www.hsa.gov.sg>)

Edoxaban

Risk of interstitial lung diseases

Japan. The MHLW and the PMDA have announced that the package insert for edoxaban (Lixiana®) has been updated to include the risk of interstitial lung disease as a clinically significant adverse reaction.

Edoxaban is used to reduce the risk of ischaemic stroke, systemic embolism, and venous thromboembolism.

Nineteen cases associated with interstitial lung diseases have

been reported in Japan. Of these, a causal relationship could not be excluded in eight cases.

Reference:

Revision of Precautions, MHLW/PMDA, 11 January 2018 (www.pmda.go.jp/english/)

Eluxadoline

Risk of pancreatitis

The United Kingdom. The MHRA has updated the Summary of Product Characteristics (SPC) and Patient Information Leaflet for eluxadoline (Truberzi®) to include the risk of pancreatitis and also to list new contraindications.

Eluxadoline is no longer indicated for use in individuals who have undergone cholecystectomy or who have biliary disorders. In addition, therapy with eluxadoline should be initiated and supervised by a physician experienced in diagnosis and management of gastrointestinal disorders.

Eluxadoline was approved in 2017 for the treatment of irritable bowel syndrome with diarrhoea in adults.

A routine European review identified 230 suspected cases of pancreatitis in patients taking eluxadoline over an estimated exposure of 26,363 patient-years. All cases of pancreatitis occurred before April 2017 when use in patients without a gallbladder became a contraindication. Of these, 76% of 140 cases with known gallbladder status were in patients who had undergone cholecystectomy and did not have a gallbladder. Four cases were severe and in two of these cases, eluxadoline appears to have contributed to the patient's death. Dehydration and pulmonary complications of acute pancreatitis have been reported in the literature.

Most of the reported cases of pancreatitis occurred within a week of starting treatment and some patients developed symptoms after one or two doses. However, cases of pancreatitis after longer duration of treatment have also been reported.

In most cases, eluxadoline treatment was withdrawn. At the time of review, out of 123 cases with an outcome reported, most (107) patients recovered from the pancreatitis or their condition improved.

Reference:

Drug Safety Update, MHRA, Volume 11, issue 5: 4, December 2017 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.2, 2017: Increased risk of serious pancreatitis in patients without a gallbladder in the USA)

Epoetins

Risk of Severe Cutaneous Adverse Reactions (SCARs)

Ireland. The Health Products Regulatory Authority (HPRA) has stated that severe cutaneous adverse reactions (SCARs) are considered to be a class effect of all epoetins.

Human endogenous erythropoietin (EPO) is a growth factor produced primarily by the kidney in response to hypoxia. There are several forms of synthetic erythropoietin (i.e. darbepoetin alfa, epoetin alfa, epoetin beta, epoetin theta, epoetin zeta and methoxy polyethylene glycol-epoetin beta) licensed for anaemias, or in the case of certain epoetins, for use before autologous blood donation, or for high-risk patients prior to specific surgeries.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recently completed a detailed analysis of SCARs associated with epoetin-containing medicines. This review was initiated following post-market reports

of SCARs including Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) with some epoetins.

The PRAC concluded that SCARs, including SJS and TEN, are considered a class effect for all epoetins and the product information for these medicines will be updated accordingly.

Reference:

Drug Safety Newsletter, HPRA, November 2017 (<https://www.hpra.ie/docs/default-source/publications-forms/newsletters/hpra-drug-safety-newsletter-edition-83.pdf?sfvrsn=5>)

The United Kingdom. The MHRA has updated the product information of all recombinant human erythropoietins (r-HuEPOs; epoetin alfa, darbepoetin alfa, epoetin beta, epoetin zeta and methoxy polyethylene glycol-epoetin beta) to reflect the risk of SCARs and to advise healthcare professionals and patients to permanently discontinue r-HuEPOs should these reactions occur.

A 2017 European review triggered by post-market reports of SCARs concluded that the class of r-HuEPOs is associated with a risk of SCARs, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

The review assessed all cases worldwide received up to February 2017, and identified a total of 23 reports of SJS and 14 reports of TEN with r-HuEPOs use. The review concluded that eight reports of SJS and one case of TEN were causally associated with r-HuEPOs. More severe cases were observed with long-acting r-HuEPOs (darbepoetin alfa and methoxy polyethylene glycol-epoetin beta). The review concluded that the risk of severe cutaneous adverse reactions was a class effect with all r-HuEPOs.

Reference:

Drug Safety Update, MHRA, Volume 11, issue 6: 2, January 2018 (www.gov.uk/mhra)

Fingolimod

1. Potential risk of thrombocytopenia

Canada. Health Canada has updated the product safety information for fingolimod (Gilenya®) to inform health-care professionals about the risk of thrombocytopenia.

Fingolimod is authorized to treat multiple sclerosis and is used in patients who have had a poor response to or, are unable to tolerate one or more other therapies for multiple sclerosis.

Health Canada reviewed the potential link between thrombocytopenia and fingolimod following reports that were received from the manufacturer.

At the time of the review, Health Canada had received 11 unique Canadian reports of thrombocytopenia suspected to be linked to the use of fingolimod. Eight reports were excluded from further review because there was not enough information. A possible link between fingolimod and thrombocytopenia was found in the remaining three reports.

This safety review also looked at information from 56 international reports and one report from the manufacturer of thrombocytopenia associated with the use of fingolimod. Forty reports were excluded from further review mainly because there was not enough information. Of the remaining 17 reports, 14 suggested a possible link between fingolimod and thrombocytopenia, and in three cases, thrombocytopenia was most likely due to other causes such as infection or another medication.

A search of the literature found some evidence of a potential link between thrombocytopenia and fingolimod use.

Health Canada's safety review concluded that there was a potential link between the use of fingolimod and thrombocytopenia.

Reference:

Summary Safety Review, Health Canada, 6 December 2017 (www.hc-sc.gc.ca)

2. Contraindications for patients with pre-existing cardiac disorders.

The United Kingdom. The MHRA has introduced new contraindications for fingolimod (Gilenya®) in patients with pre-existing cardiac disorders.

A routine EU review identified 44 post-market global reports of serious ventricular tachyarrhythmia and six reports of sudden death in patients taking fingolimod up to the end of February 2017. To this date, the cumulative post-market exposure to fingolimod was estimated to be 397,764 patient-years. The review recommended that warnings against the use of fingolimod in patients with underlying cardiac disorders should be strengthened and listed as a contraindication for use.

Reference:

Drug Safety Update, MHRA, Volume 11, issue 5: 5, December 2017 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.6, 2017: Contraindicated in patients with underlying cardiac pathology and risks of skin neoplasms in Spain)

Flucloxacillin and concomitant paracetamol

Interaction: Risk of high anion gap metabolic acidosis

Ireland. The HPRA has stated that the SPC and package leaflet for flucloxacillin-containing medicinal products will be updated to include

information on the risk of high anion gap metabolic acidosis (HAGMA) and concomitant paracetamol therapy.

Flucloxacillin containing medicinal products are licensed for the treatment of specified bacterial infections.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recently concluded a review of the risk of HAGMA with flucloxacillin and concomitant paracetamol therapy. Evidence in the literature and a limited number of spontaneous reports seem to support the possibility of the appearance of a specific type of HAGMA (pyroglutamic acidosis) in the presence of flucloxacillin and paracetamol.

Reference:

HPRA Drug Safety Newsletter, 83rd edition, 30 November 2017 (<http://www.hpra.ie/docs/default-source/publications-forms/newsletters/hpra-drug-safety-newsletter-edition-83.pdf?sfvrsn=5>)

Gadolinium-based contrast agents (GBCAs)

Gadolinium retention in body

Japan. The MHLW and the PMDA have announced that the package inserts for gadolinium-based contrast agents (GBCAs) have been updated to include information on minimizing potential risks associated with retention of gadolinium in brain tissues.

GBCAs are used with magnetic resonance imaging (MRI) for diagnosis of certain diseases. GBCAs contain gadolinium, a heavy metal.

After investigating the literature and case reports for information about retention of gadolinium in brain tissue, the PMDA has confirmed that gadolinium remains in the

brain tissue after use. However, there has been no clear evidence of clinical symptoms related to gadolinium retention in the brain occurring in patients. It is not known in the long-term if gadolinium retention in the brain can lead to delayed adverse reactions including nerve disorders.

It has been reported that gadolinium retention in the brain is mostly confirmed with linear GBCAs and there is less deposit in the brain tissues in patients who have received macrocyclic GBCAs. Thus, it is considered appropriate to use macrocyclic GBCAs preferentially when MRI scans with GBCAs are required and to use linear GBCAs when macrocyclic GBCAs are not appropriate for the patients for reasons including the incidence of adverse reactions.

Reference:

Revision of Precautions, MHLW/PMDA, 28 November 2017 (www.pmda.go.jp/english/)

USA. The US FDA has required several actions to alert health-care professionals and patients about gadolinium retention after a MRI using GBCA, and actions that can help minimize problems. These include requiring a new patient medication guide and providing educational information that every patient will be asked to read before receiving a GBCA. The FDA has also required manufacturers of GBCAs to conduct human and animal studies to further assess the safety of these contrast agents.

To date, the only known adverse health effect related to gadolinium retention is a rare condition called nephrogenic systemic fibrosis (NSF) that occurs in a small subgroup of patients with pre-existing kidney failure. The FDA received reports of adverse events involving multiple organ systems in patients with normal kidney function. A causal association between these adverse events and

gadolinium retention could not be established.

Gadolinium retention has not been directly linked to adverse health effects in patients with normal kidney function, and the FDA has concluded that the benefit of all approved GBCAs continues to outweigh any potential risks. However, after additional review and consultation with the Medical Imaging Drugs Advisory Committee, the FDA is requiring several actions as above.

Reference:

Safety Alerts for Human Medical Products, US FDA, 19 December 2017 (www.fda.gov)

(See WHO Pharmaceuticals Newsletters No.5, 2017: Retention of gadolinium in the brain in New Zealand, No.4, 2017: Restrictions on use in EU, No harmful effects identified with brain retention in the USA and No.5, 2015: Possible risk of brain deposits with repeated use in the USA)

Idelalisib

Risk of a rare brain infection (progressive multifocal leukoencephalopathy)

Canada. Health Canada has updated the product safety information for idelalisib (Zydelig®) to warn health-care professionals and patients about the risk of progressive multifocal leukoencephalopathy (PML).

Idelalisib is a prescription drug authorized to treat certain types of blood cancer.

Health Canada reviewed the potential risk of PML with idelalisib use.

The review identified nine international reports of PML in patients treated with idelalisib. In eight of the nine reports, the link between PML and the use of idelalisib was considered to be possible. However, other factors such as the type of cancer being treated, concomitant medicines and medication history also played

a role in causality. The remaining report could not be assessed because there was not enough information. There were no Canadian reports of PML linked to the use of idelalisib at the time of the review.

A possible link between idelalisib use and PML could be explained by the actions of idelalisib on the immune system. Idelalisib is known to suppress the immune system and PML occurs generally in patients that have a weak immune system.

Health Canada's review concluded that there was a possible link between idelalisib and PML.

Reference:

Summary Safety Review, Health Canada, 15 December 2017 (www.hc-sc.gc.ca)

(See No.2, No.1, 2017 and No.5, No.4, No.3 and No.2 in 2016 for related information)

Iodine-containing contrast agents

Possible risk of hypothyroidism in infants

New Zealand. The Medicines and Medical Devices Safety Authority (Medsafe) has requested that data sheets for iodine-containing contrast agents (ICAs) are updated with information on the risk of hypothyroidism. The data sheets should include information on thyroid function and monitoring, particularly in neonates.

ICAs are medicines used to enhance visibility of blood vessels and organs during medical imaging (e.g. CT scans). ICAs can be administered intravascularly or enterally.

Medsafe put ICAs under its medicine monitoring programme on 2 March 2017.

During the period (2 March to 30 September 2017), one case of hypothyroidism was reported in a premature newborn to the

Centre for Adverse Reactions Monitoring (CARM). A thyroid-stimulating hormone (TSH) test at three days of age was normal, but TSH was elevated about two weeks after a single dose of ICA. Iodine levels in the urine were high approximately 20 days after ICA was given.

The balance of benefits versus harm for ICAs remains positive and no further action is required at this time.

Reference:

Safety Information, Medsafe, 5 December 2017 (www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletters No.2, 2017: Possible risk of hypothyroidism in infants: added to the medicines monitoring scheme in New Zealand and No. 6, 2015: Rare cases of underactive thyroid in infants in the USA)

Ipilimumab

Risk of myositis

Japan. The MHLW and the PMDA have announced that the package insert for ipilimumab (Yervoy®) has been updated to include the risk of myositis as a clinically significant adverse reaction.

Ipilimumab is indicated for unresectable malignant melanoma.

Two cases associated with myositis have been reported in Japan. A causal relationship could not be excluded in any of these cases. The decision to change the package insert was made after considering information on precautions and mechanisms of action in the EU and US package inserts; and after reviewing cases of myositis reported in patients using ipilimumab overseas.

Reference:

Revision of Precautions, MHLW/PMDA, 11 January 2018 (www.pmda.go.jp/english/)

Lenvatinib

Risk of acute cholecystitis

Japan. The MHLW and the PMDA have announced that the package insert for lenvatinib (Lenvima®) has been updated to include the risk of acute cholecystitis as a clinically significant adverse reaction.

Lenvatinib is indicated for unresectable thyroid cancer.

Eleven cases associated with acute cholecystitis have been reported in Japan. Of these, a causal relationship could not be excluded in four cases. The company core datasheet (CCDS) has also been updated.

Reference:

Revision of Precautions, MHLW/PMDA, 11 January 2018 (www.pmda.go.jp/english/)

Long-acting beta agonists (LABAs) and inhaled corticosteroids (ICS)

Removal of Boxed Warning about asthma related deaths

USA. The US FDA has removed the boxed warning about asthma-related deaths from the drug labels of medicines that contain both an inhaled corticosteroids (ICS) and long-acting beta agonists (LABAs).

LABAs are inhaled medications that are used in the treatment of asthma and chronic obstructive pulmonary disease (COPD).

ICS are indicated for the maintenance treatment of asthma as prophylactic therapy in adult and paediatric patients six years of age and older. It is also indicated for asthma patients requiring oral corticosteroid therapy, where adding ICS may reduce or eliminate the need for oral corticosteroids.

A FDA review of four large clinical safety trials shows that treating asthma with LABAs in

combination with ICS does not result in significantly more serious asthma-related adverse effects than treatment with ICS alone. A description of the four trials has also been included in the warnings and precautions section of the drug labels.

Reference:

Safety Alerts for Human Medical Products, US FDA, 19 December 2017 (www.fda.gov)

Opioid cough and cold medicines (prescription)

Limited use: Only for adults of 18 years of age and older

USA. The US FDA has required that labels for prescription cough and cold medicines containing codeine or hydrocodone are updated to include limitations of use. These products are restricted and should be used only for adults of 18 years of age and older as risks outweigh benefits when used in adolescents and children younger than 18 years of age. The FDA also requires that information about the risks of misuse, abuse, addiction, overdose, death, and slowed or difficult breathing are added to the boxed warnings for prescription cough and cold medicines containing codeine or hydrocodone.

Codeine and hydrocodone are available in combination with other medicines, such as antihistamines and decongestants, in prescription medicines to treat coughs and symptoms associated with allergies or the common cold. Other non-opioid prescription and over the counter (OTC) medicines are available to treat these symptoms.

The FDA has taken this action after conducting an extensive review and convening a panel of external experts.

Reference:

Safety Alerts for Human

Medical Products, US FDA, 11 January 2018 (www.fda.gov)

(See WHO Pharmaceuticals Newsletters No.6, No.4, No.3, No.2 and No.1, 2017, No.5 and No.1 in 2016, No.6, No.5, No.4 and No.3 in 2015 for related information)

Paracetamol (modified-release) containing products

Suspension in EU market: due to difficulty in managing overdose

Europe. The Coordination Group for Mutual Recognition and Decentralised Procedures - Human (CMDh) has endorsed the recommendation by the European Medicines Agency (EMA) to suspend marketing of modified- or prolonged-release products containing paracetamol.

Paracetamol is widely used to relieve pain and fever in adults and children.

CMDh agreed with the Agency's advice that the advantages of a longer-acting product did not outweigh the complications of managing an overdose of the medicine, since the treatment procedures for immediate-release products are not appropriate for modified-release paracetamol.

The medicines will remain suspended unless the companies that hold the marketing authorisations can provide evidence of appropriate and practical EU-wide measures to help prevent overdose with these products and adequately reduce its risks.

Immediate-release paracetamol products, which are not affected by this decision, will continue to be available as before.

Reference:

News and press releases, EMA, 15 December 2017 (www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletter No.5, 2017: Modified- or prolonged-release preparations should be suspended from marketing in EU)

Proton Pump Inhibitors (PPIs)

Risk of subacute cutaneous lupus erythematosus (SCLE)

Canada. Health Canada has updated the product safety information for all proton pump inhibitors (PPIs) to inform health-care professionals and patients about the rare risk of subacute cutaneous lupus erythematosus (SCLE).

PPIs are medications used to reduce stomach acid, treat heartburn and sores in the lining of the stomach. They are available with a prescription and over-the-counter.

Health Canada reviewed the potential risk of SCLE after an article indicating the risk of SCLE with PPIs was published in the literature.

As of September 30, 2016, Health Canada received two Canadian reports of potential SCLE with PPI use, but there were insufficient information in these reports to show that the patients had all the symptoms suggestive of SCLE or to conclude that the PPI caused the skin reaction.

Health Canada reviewed another 18 international reports of potential SCLE with PPI use in the published literature. Other factors may have contributed to the skin reaction, e.g. concomitant medicines. It was noted that, of these patients, 16 recovered when they stopped taking the suspected PPI.

SCLE cases have not been reported for all PPIs. However, it is expected that all PPIs could potentially lead to the development of SCLE in some individuals.

Health Canada concluded that there is a rare risk of SCLE associated with PPI use.

Reference:

Summary Safety Review,

Health Canada, 5 December 2017 (www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletter No.5, 2015: Very low risk of subacute cutaneous lupus erythematosus in the United Kingdom)

Sedative and anaesthetic drugs (other than benzodiazepines and barbiturates)

Risk of neurodevelopmental disorders

Canada. Health Canada has updated the product information for specific sedative and anaesthetic drugs (propofol, ketamine, sevoflurane, desflurane, and isoflurane) to warn health-care professionals and patients about the risk of neurodevelopmental disorders.

Sedative and anaesthetic drugs are used by health-care professionals during surgical and medical procedures in children and adults.

Health Canada carried out a safety review to assess the potential for negative effects on the development of children's brains (i.e. neurodevelopmental disorders) with specific sedative and anaesthetic drugs (propofol, ketamine, sevoflurane, desflurane and isoflurane) used in early childhood or in pregnant women (exposure of the fetus).

At the time of the review, Health Canada searched for Canadian and international reports for potential negative effects on the development of children's brains related to the use of sedative and anaesthetic drugs in pregnant women or young children. In the identified reports (39 Canadian and 38 international), two reports of international patients were of interest but there was not enough information to further assess these reports.

Published studies in animals suggest that repeated or lengthy exposure (more than

three hours) to sedative and anaesthetic medicines during the third trimester of pregnancy or in young animals can cause neurodevelopmental issues, such as problems with learning and memory. In contrast, neurodevelopmental issues were not seen when animals were treated for a shorter period of time (three hours).

Published studies, mostly in children up to three years of age, were also found. In these studies, some found no link between the use of these drugs and neurodevelopmental disorders while others found similar results as those seen in the animal studies. However, in studies on children, it was not clear whether the neurodevelopmental disorder was due to the drug or other factors such as illness or the surgery itself.

Health Canada's review concluded that repeated or lengthy use (more than three hours) of these sedative and anaesthetic drugs in pregnancy and in children up to approximately three years of age may potentially lead to neurodevelopmental disorders in children.

Reference:

Summary Safety Review, Health Canada, 22 December 2017 (www.hc-sc.gc.ca)

(See page -13- and WHO Pharmaceuticals Newsletters No.3, 2017: Potential risk of effects on development of children's brains in the USA and No.1, 2017: Potential risk of effects on development of children's brains in the USA)

Tacrolimus products (oral)

To prescribe and dispense by brand name only

The United Kingdom. The MHRA has reminded health-care professionals that all oral tacrolimus products should be prescribed and dispensed by brand name only.

Tacrolimus is given orally to prevent or treat organ transplant rejection.

The MHRA is aware of new oral tacrolimus products that are about to be launched or are already on the market. Recommendations from June 2012 remain in place, and also apply to any new tacrolimus products launched. This includes generic products and prolonged-release formulations.

Tacrolimus has a narrow therapeutic index, and even minor differences in blood levels have the potential to cause graft rejection reactions or toxicity. Inadvertent switching between tacrolimus products has been associated with reports of toxicity and graft rejection. Health-care professionals are advised to ensure patients receive careful supervision and therapeutic monitoring by an appropriate specialist if the brand of tacrolimus is switched.

Reference:

Drug Safety Update, MHRA, Volume 11, issue 4: 3, November 2017 (www.gov.uk/mhra)

Teriparatide

Risk of cardiac arrest, respiratory arrest and loss of consciousness accompanying seizures

Japan. The MHLW and the PMDA have announced that the package inserts for teriparatide preparations (Teribone® and Forteo®) have been updated to include the risks of cardiac arrest, respiratory arrest and loss of consciousness accompanying seizures.

Teriparatide is indicated for osteoporosis with high risk of bone fracture.

Three cases associated with cardiac and respiratory arrest, and 44 cases of loss of consciousness have been reported in Japan. Of these, a causal relationship could not be

excluded in two and 40 cases,
respectively.

Reference:

Revision of Precautions,
MHLW/PMDA, 11 January 2018
(www.pmda.go.jp/english/)

Antiepileptic drugs

Advice on switching between different manufacturers' products

The United Kingdom. The MHRA has reminded health-care professionals to consider that antiepileptic medicines vary in characteristics which influences the risk of whether switching between different brands may cause adverse effects or loss of seizure control.

Antiepileptic medicines can be classified into three main categories. Advice about switching for each category has been given, for example patients taking carbamazepine, (a category one medicine) should be maintained on a specific manufacturers product. Other advice on considerations that should be taken for patient related factors such as negative perceptions and clinical factors such as seizure frequency, have been highlighted for switching medicines in categories two and three.

Reference:

Drug Safety Update, MHRA, Volume 11, issue 4: 4, November 2017 (www.gov.uk/mhra)

Benzodiazepines and barbiturates

Risk of neurodevelopmental disorders: not enough evidence

Canada. Health Canada has carried out a safety review to assess the potential development of neurodevelopmental disorders with the use of benzodiazepines and barbiturates (lorazepam, midazolam, phenobarbital and thiopental) when used in early childhood (up to and including five years of age) or during pregnancy (exposure of the fetus).

Benzodiazepines and barbiturates are sedative and anaesthetic medicines and are often required during surgery and medical procedures in children and adults.

At the time of the review, Health Canada searched for Canadian and international cases that reported effects of benzodiazepine and barbiturate exposure to fetus in pregnant women or in young children on the development of children's brains. There were a total of 137 Canadian reports and 110 international reports. However, due to multiple factors (e.g. symptoms described in the reports did not meet the definition of neurodevelopmental disorders) it was not possible to draw conclusions from these reports.

Animal studies in pregnant or young animals did not show consistent evidence of negative effects on the development of children's brains with the use of benzodiazepines and barbiturates medicines.

Health Canada's review of the available information concluded that there is limited evidence suggesting a link between the use of benzodiazepines and barbiturates and neurodevelopmental disorders.

Reference:

Summary Safety Review, Health Canada, 22 December 2017 (www.hc-sc.gc.ca)

(See also page -11-)

Chlorhexidine

Risk of serious allergic reactions

Singapore. The HSA has informed health-care professionals about the outcome of a review on the known risk of allergic reactions, whilst using chlorhexidine-containing products.

Chlorhexidine is a broad-spectrum antiseptic which is effective against gram-positive and gram-negative bacteria on

the skin and is widely used to reduce the risk of bacterial infections.

This review was conducted following safety alerts of serious allergic reactions reported with antiseptic products containing chlorhexidine.

Fifteen reports of anaphylactic reactions related to chlorhexidine were identified over a span of 36 years (1981 to 2017). There was no increase in trend of serious allergic reactions to chlorhexidine-containing products observed. At the time of the review, HSA did not identify any significant safety signals regarding serious allergic reactions with the use of chlorhexidine in Singapore.

Health-care professionals are advised to inform patients to stop using the product and seek immediate medical attention if they experience symptoms of a serious allergic reaction, such as wheezing, swelling of the face, or severe rashes.

Reference:

Product Safety Alerts, HSA, 29 September 2017 (<http://www.hsa.gov.sg>)

Ibuprofen

Study suggests effects on testicular physiology

France. L'Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) has reminded health-care professionals and patients about the importance of respecting the treatment dosage and duration defined in the marketing authorisation for ibuprofen. The lowest effective dose for the shortest time necessary to address patients' symptoms should be used.

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) used primarily for pain and fever.

This reminder follows results of a study conducted in Denmark on the effects of ibuprofen on testicular physiology.

Results from a study suggest that ibuprofen taken in large doses for prolonged periods can disrupt testicular physiology. However, testosterone levels observed in study participants remained normal. In addition, no clinical consequences (male fertility disorders, impotence, libido disorders) were found.

This study is being analyzed at European level to determine, if further studies are needed.

At this stage, these results do not alter the benefit/risk ratio of ibuprofen when used in accordance with its marketing authorization.

Reference:

Point d'information, ANSM, 10 January 2018, France (www.ansm.sante.fr)

Interferon beta-1a

Risk of Sarcoidosis: not enough evidence

Canada. Health Canada has reviewed the potential risk of sarcoidosis linked to the use of interferon beta-1a (Avonex®) after reviewing international reports of sarcoidosis with interferon beta-1a use.

Interferon beta-1a is a prescription medicine used for the treatment of various forms of multiple sclerosis (MS).

At the time of the review, Health Canada had not received any Canadian reports of sarcoidosis in MS patients who had been treated with interferon beta-1a.

This safety review looked at 81 international cases of sarcoidosis reported with the use of interferon beta-1a use in the WHO's global database of Individual Case Safety Reports. Almost all cases were considered serious by the reporters. Only five reports had

enough information for further assessment, one of which was found to be directly linked to treatment with interferon beta-1a.

The manufacturer also provided 102 international reports of sarcoidosis with interferon beta-1a use. Among these, 15 reports met the criteria for further assessment by Health Canada. Although 14 of the 15 reports were considered possibly linked to interferon beta-1a, none were found to be directly linked to its use.

A search of the scientific literature identified 10 reports of sarcoidosis in patients who had been treated with interferon beta-1a. A link between sarcoidosis and interferon beta-1a could not be made.

Health Canada's review of the available information did not find a link between the use of interferon beta-1a and the risk of sarcoidosis.

Reference:

Summary Safety Review, Health Canada, 8 January 2018 (www.hc-sc.gc.ca)

Quinine

Dose-dependent QT-prolonging effects and interactions with other medicines

The United Kingdom. The MHRA has reminded health-care professionals of dose-dependent QT-interval-prolonging effects associated with quinine use. Quinine should be used with caution in patients with QT prolongation risk factors (e.g. pre-existing cardiac disease) or in those with atrioventricular block.

Quinine has been used for the treatment of nocturnal leg cramps in the United Kingdom.

Quinine is metabolised via hepatic oxidative cytochrome P450 pathways, predominantly

by CYP3A4. A review in 2017 identified a pharmacokinetic study reporting that serum levels of phenobarbital or carbamazepine can be raised with concomitant quinine use. Although data appear to be limited, it is advisable to monitor for evidence of toxicity if quinine is used concomitantly with these anticonvulsant medicines.

Reference:

Drug Safety Update, MHRA, Volume 11, issue 4: 2, November 2017 (www.gov.uk/mhra)

Radium-223 dichloride in combination with abiraterone and prednisone/prednisolone

Risk of death and fractures

The United Kingdom. The MHRA has advised health-care professionals not to treat patients with radium-223 dichloride (Xofigo®) in combination with abiraterone acetate and prednisone/prednisolone due to risk of death and fractures.

Radium-223 dichloride is licenced for the treatment of men with castration-resistant prostate cancer, symptomatic bone metastases, and no known visceral metastatic disease.

Preliminary data from a randomised, double-blind, placebo-controlled study showed an increased incidence of deaths and fractures among patients receiving radium-223 dichloride in combination with abiraterone acetate and prednisone/ prednisolone compared to patients receiving placebo in combination with abiraterone acetate and prednisone/prednisolone. This study in asymptomatic or mildly symptomatic chemotherapy-naive patients with bone-predominant metastatic castration-resistant

prostate cancer was unblinded early based on an Independent Data Monitoring Committee recommendation.

Reference:

Drug Safety Update, MHRA, Volume 11, issue 5: 3, December 2017 (www.gov.uk/mhra)

Rolapitant

Risk of anaphylaxis and other serious hypersensitivity reactions

USA. The US FDA has warned health-care professionals that anaphylaxis and other serious hypersensitivity reactions with the use of rolapitant (Varubi®) have been reported.

Rolapitant is used to prevent delayed phase chemotherapy-induced nausea and vomiting (emesis) in combination with other antiemetic medicines.

Anaphylaxis, anaphylactic shock and other serious hypersensitivity reactions have occurred during or soon after the infusion of rolapitant injectable emulsion. Most reactions have occurred within the first few minutes of administration. Symptoms of anaphylaxis can include wheezing or difficulty breathing; swelling of the face or throat; hives or flushing; itching; abdominal cramping, abdominal pain or vomiting; back pain or chest pain; hypotension or shock.

Healthcare professionals must be vigilant for signs of hypersensitivity or anaphylaxis in all patients receiving rolapitant injectable emulsion, both during and following its administration.

Reference:

Safety Alerts for Human Medical Products, US FDA, 16 January 2018 (www.fda.gov)

SGLT2 inhibitor

Risk of non-traumatic amputations of the lower limbs, diabetic ketoacidosis and renal failure

Chile. El Instituto de Salud Pública de Chile is updating the safety information brochures for pharmaceutical products containing SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin), to reflect cases of non-traumatic amputations of lower limbs (amputation of toes associated with canagliflozin use), diabetic ketoacidosis and acute renal failure.

SGLT2 inhibitors are used for type 2 diabetes mellitus.

Reference:

Boletín N°11 de Farmacovigilancia, Instituto de Salud Pública de Chile, January 2018 (www.ispch.cl)

(See WHO Pharmaceuticals Newsletters No.3 and No.2, 2017, No.4, No.3, No.3 and No.1 in 2016 and No.6, No.5, No.4 in 2015 for related information)

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 16 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. Signals are first communicated to National Pharmacovigilance Centres through SIGNAL (a restricted document from UMC), 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 27). 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, 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.

Ciprofloxacin, enalapril and acute kidney injury: strengthening of a drug interaction signal

Dr Ruth Savage, Uppsala Monitoring Centre and New Zealand

Summary

A case series of 16 reports in VigiBase, the WHO global database of individual case safety reports, of acute kidney injury (AKI) associated with enalapril and ciprofloxacin as co-suspect or interacting medicines was identified through statistical screening for suspected drug interactions. The suspected interaction is unlabelled. Use of enalapril, an angiotensin converting enzyme (ACE) inhibitor, may lead to renal impairment due to altered renal haemodynamics in particular clinical situations or with other medicines that affect renal glomerular filtration. Increased serum creatinine and blood urea nitrogen have been observed in ciprofloxacin users and AKI has been reported in approximately 1 in 1,500 patients. Clinical assessment of the VigiBase reports identified 11 patients for whom a direct renal effect of ciprofloxacin alone or interacting with enalapril was the most likely explanation for AKI. In the remaining five reports an alternative explanation was more likely. Most of the patients in the 11 reports that supported causality had characteristics that increased their risk of renal failure, including patients aged over 80 years with two or more risk factors for ACE inhibitor-related renal failure. Despite their high risk most patients did not develop AKI until ciprofloxacin was added to their regime. A nested case-control study in a cohort of older male patients admitted to hospital for AKI demonstrated a 2-fold greater risk for AKI with fluoroquinolones compared with no use and a 4.6-fold increase in risk for fluoroquinolones combined with renin-angiotensin blockers. This observation is in keeping with the VigiBase

disproportionality measure for ciprofloxacin and enalapril.

The observed versus expected values for AKI with two other ACE inhibitors and ciprofloxacin as co-suspect or interacting also supported an ACE inhibitor class effect. There were insufficient reports to assess other fluoroquinolones.

Although the mechanism is unclear, three observations support this signal. The two statistical observations from the published case-control study and from VigiBase and, thirdly, the onset of AKI after ciprofloxacin was added to the regimes of patients taking enalapril most of whom were already at high risk of AKI. This signal suggests further investigation is needed to ascertain if there is an additional risk of nephrotoxicity with ciprofloxacin in patients taking an ACE inhibitor.

Introduction

A signal detection screening focusing on drug-drug interactions identified disproportionate reporting of a combination of ciprofloxacin, enalapril and acute kidney injury (AKI) in VigiBase, the WHO global database of individual case safety reports.

A range of pre-renal, renal and post-renal clinical conditions can lead to AKI. Drugs can be involved at any of these levels and so may cause conditions leading to pre-renal injury by

volume depletion e.g. through haemorrhage or dehydration, or through a direct effect on glomerular arteriolar pressures. Drug-induced direct renal toxicity e.g. due to interstitial nephritis or acute tubular necrosis is well-recognised. Promotion of renal stone formation can lead to post-renal obstruction and AKI.

Ciprofloxacin is a broad spectrum fluoroquinolone antibiotic. It has been estimated that about 1 in 1,500 patients develop AKI after taking ciprofloxacin.¹ The underlying pathology identified through published case histories was interstitial nephritis in most patients.² There have also been reports of increased serum creatinine and blood urea nitrogen and, more rarely, crystalluria and macrohaematuria.³ As a broad spectrum antibiotic, it can also cause diarrhoea which may lead to dehydration and AKI in susceptible patients.

Enalapril is an angiotensin converting enzyme (ACE) inhibitor used to reduce blood pressure and treat cardiac failure. ACE inhibitors decrease the production of angiotensin II, a substance which causes post-glomerular arteriolar constriction thus maintaining glomerular capillary filtration. Usually pre-glomerular arteriolar pressures are high enough for adequate filtration in the presence of ACE inhibition but drugs and clinical conditions that affect renal blood flow and pre-glomerular arteriolar pressures may trigger renal failure in patients taking ACE inhibitors. These include concomitant use of loop, thiazide or potassium-sparing diuretics, and prostaglandin inhibitors (NSAIDs), renal artery stenosis, renal transplant, old age, ischaemic heart disease and congestive heart failure, sodium restriction, sodium depletion, volume depletion, hypotension and gastrointestinal fluid loss.⁴

Reports in Vigibase

As of 14 September 2016, Vigibase holds 16 reports that include ciprofloxacin and enalapril as suspect or interacting medicines and the MedDRA preferred term acute kidney injury. At the time of the signal detection screening the number of reports in this combination was 15 with an expected number of only two. The UMC measure of disproportionate reporting for drug-drug interactions (Ω)⁵ in Vigibase was 2.38 for Ω and 1.56 for the lower limit of the 95% credibility interval, $\Omega_{0.25}$.

The 16 reports are from six countries, eight from Spain, two each from Italy, Switzerland and the United States (US), and one each from Germany and Sweden. No duplicates were detected.

Table 1 shows the report details. There were eight males and eight females. The age range was 42 to 97 years with a median of 77.5 years. Patient characteristics included background chronic renal failure (CRF) in six patients. The indication for ciprofloxacin was urinary tract infection, cystitis or prostatitis for eight patients, four of whom had CRF. The time to onset of AKI from commencement of ciprofloxacin, recorded for 13 patients, was 0 to 43

days with a median of 5.5 days. Most patients had taken ciprofloxacin for two weeks or less. The route of administration was oral (13 patients) and the daily dose (six patients) 500 or 1000 mg. For enalapril, complete administration dates were recorded for six patients, four were long term users and two short term. The patients in the remaining reports were also long term users with the start date unknown. The route of administration was oral (13 patients). Daily doses (eight patients) were within the recommended range of 2.5 to 20 mg, with one outlier taking 50 mg.

Assessment of individual case reports indicated a more likely alternative reason for AKI than a nephrotoxic effect of ciprofloxacin with enalapril in five patients (cases 12-16). These were dronedarone-related AKI (12), Lyell's syndrome attributed to allopurinol or, less likely, ciprofloxacin (13), sepsis, pancytopenia and AKI with multiple antibiotics (14), AKI after multiple antibiotics for chemotherapy-related infection (15), a combined effect of metamizole, an NSAID, added to furosemide and enalapril two days prior to AKI onset with ciprofloxacin commenced on the day of AKI onset (16).

Analysis of cases 1 to 11 in Table 1 indicated that in most patients although clinical conditions and a number of medicines were likely to have increased their risk of AKI, including ACE inhibitor-related AKI, the event did not occur until after a recent ciprofloxacin prescription lending weight to ciprofloxacin being the cause or a combined action of ciprofloxacin and enalapril.

Enalapril was used long term in nine patients and ciprofloxacin use was short term in all eleven. Co-suspect medicines with enalapril and ciprofloxacin were recorded in 10 of the 11 reports and included NSAIDs (2, 8) and diuretics (3, 4, 5, 6, 11). All but one case was recorded as serious. At least five patients were admitted and four had prolonged hospital stays. After suspect medicines were stopped, ten patients recovered or were recovering and one died of cardiac failure eight days later.

Three case reports (1, 7 and 10) are key reports. In case report 1 metformin was also suspect but it had been taken for two months and appears unlikely to have contributed. The patient in case report 7 had CRF and had taken bisoprolol, also suspect, for several months but renal impairment is not a labelled adverse drug reaction for this medicine. The patient recovered from AKI when all three medicines were discontinued. Patient 10 was also taking omeprazole, a known cause of interstitial nephritis, but he recovered when enalapril and ciprofloxacin were withdrawn and omeprazole continued.

Table 1. Characteristics of case reports in VigiBase of acute kidney injury (AKI) in association with ciprofloxacin and enalapril

Case	Age/ Sex	Suspect (S) or interacting (I) drugs	Daily dose	Route	Time to onset of AKI	Indication	Concomitant medicines	Co-reported ADRs	Relevant medical history	Dechallenge, outcome	Comment
1	52/F	Enalapril, ciprofloxacin, metformin (all I)	50 mg 1000 mg 1700 mg	Oral Oral Oral	LT* 6 days 2 months	Hypertension UTI** T2DM***	Clonazepam	-	Hypertension, diabetes	All suspects discontinued, recovering	-
2	87/M	Enalapril, ciprofloxacin, ibuprofen, pravastatin (all I)	- - - -	Oral Oral Oral Oral	LT 5 days LT LT	Hypertension UTI - Hyperlipidaemia	Rivaroxaban, risperidone	Diarrhoea, speech and walking problems, blood glucose uncontrolled	CRF****, diarrhoea	All suspects discontinued, recovered	Profuse diarrhoea 2 days after starting ciprofloxacin
3	74/M	Enalapril, ciprofloxacin, metolazone, torasemide, methotrexate (all S)	20 mg - 5 mg/week 5 mg One dose weekly	Oral Oral Oral Oral SC	LT 12 days LT LT LT	- - - - -	Acenocoumarol, bisoprolol, glimepiride, metformin, simvastatin, deflazacort, pantoprazole, oxazepam	-	Septic arthritis, cardiomyopathy, T2DM, peripheral obliterating arteriopathy	All suspects discontinued, improved then relapsed. Metformin discontinued, recovering.	Abdominal sonography normal
4	94/F	Enalapril, ciprofloxacin, furosemide (all S)	5 mg - -	Oral Oral Oral	6 months 5 days 13 days	Hypertension Bronchitis Cardiac decompensation	Glyceryl trinitrate, folic acid, tiotropium, fluticasone/salmeterol, acetylsalicylic acid, lorazepam, colecalfiferol, mirtazapine, omeprazole	Diarrhoea, vomiting, hyponatraemia	-	All suspects discontinued, recovering	-
5	61/M	Enalapril, ciprofloxacin, furosemide (all I)	- - -	Oral Oral Oral	7 days 7 days 7 days	Hypertension UTI Hypertension	-	Dehydration	Hypertension	All suspects discontinued, recovered	-
6	85/F	Enalapril, ciprofloxacin, hydrochlorothiazide (all I)	20 mg 1.0 g 12.5 mg	Oral Oral Oral	LT 6 days 2-3 months	Hypertension Bronchitis or gastroenteritis Hypertension	Metformin, trimetazidine, simvastatin, alprazolam, ipratropium, omeprazole	Nausea, vomiting, hypoxia, hypotension, tachycardia, tachypnoea	Hypertension, dyslipidaemia, T2DM, glaucoma, dizziness, acute bronchitis	All suspects discontinued, recovered	-
7	89/M	Enalapril, ciprofloxacin, bisoprolol (all I)	- - -	Oral Oral Oral	9-21 months 4 days 9-21 months	Hypertension Prostatitis -	Paracetamol, alprazolam, ranitidine	-	CRF	All medicines discontinued, recovered	-
8	62/M	Enalapril, ciprofloxacin, ibuprofen (all S)	- - -	- - -	LT 0-24 days 0-24 days	Hypertension UTI "Trouble with knee"	-	Serum creatinine 300 mmol/L	Hypertension 25 years treated with beta blocker, diuretic and ACE inhibitor. Unclear if first two current.	All suspects discontinued, recovering	Renal CT and ultrasound scan normal
9	86/M	Enalapril, ciprofloxacin, acetylsalicylic acid, amoxicillin/ clavulanate (all I)	5 mg 1000 mg 300 mg -	Oral Oral Oral Oral	LT 4 days LT 4 days	Cardiomyopathy Bacterial respiratory infection Cardiomyopathy Bacterial respiratory infection	Furosemide, paracetamol	-	CRF	All medicines discontinued. Treated with frusemide and dopamine. Died.	Died due to cardiac failure 8 days after medicines were discontinued
10	63/M	Enalapril, ciprofloxacin (both I)	20 mg 1000 mg	Oral Oral	5-17 months 6 days	Hypertension UTI	Omeprazole, pentoxifylline	-	Hypertension	Both suspects discontinued, recovering	Renal artery stenosis on Doppler ECHO but arteriography normal
11	73/M	Enalapril, ciprofloxacin, furosemide (all S)	2.5 mg 1000 mg 125 mg	Oral Oral Oral	5 days 11 days -	Heart disease complications Bronchopneumonia Heart disease complications	Triazolam, digoxin	-	-	All suspects discontinued, recovered	-
12	81/F	Enalapril, ciprofloxacin, dronedaron, sitagliptin, acenocoumarol (all S)	5 mg 500 mg 400 mg - -	Oral Oral Oral Oral Oral	- 43 days - - -	Hypertension Cystitis Atrial fibrillation T2DM Atrial fibrillation	Insulin	-	CRF, T2DM, bladder cancer, macrohaematuria	Sitagliptin and enalapril discontinued and vessel resection, no improvement. Dronedaron discontinued, recovering.	Conflicting information for ciprofloxacin discontinuation
13	83/F	Enalapril, ciprofloxacin, allopurinol, moxifloxacin (all S)	20 mg - 300 mg -	Oral Oral Oral IV	- 3 days - 0 days	- Infected scar - -	-	Lyell's syndrome or paraneoplastic syndrome	CRF, renal anaemia, hypertension, hyperuricaemia, adenocarcinoma, infected biopsy	All suspects discontinued, outcome unknown	-
14	54/F	Enalapril, ciprofloxacin, allopurinol, metformin, telavancin, cefepime, amoxicillin/clavulanate, ceftriaxone (all S)	- - - - - - -	- - - - IV - - parenteral	- - - - 17 days - - 30 days	- - - - Osteomyelitis - - Diabetic foot	-	Klebsiella infection, diarrhoea, hypertensive heart disease, osteomyelitis, sepsis, pneumonia, cellulitis, tubulo-interstitial nephritis, pancytopenia	Hypertension, gout, dyslipidaemia, uncontrolled diabetes	All suspects discontinued, recovered	Leucopenia after telavancin and cefepime, then pancytopenia after all other antibiotics

Case	Age/ Sex	Suspect (S) or interacting (I) drugs	Daily dose	Route	Time to onset of AKI	Indication	Concomitant medicines	Co-reported ADRs	Relevant medical history	Dechallenge, outcome	Comment
15	42/F	Enalapril, ciprofloxacin, paclitaxel, carboplatin, oxacillin, vancomycin (all S)	- - 340 mg 703 mg - -	- - IV IV - -	- - 12 days 12 days - -	Hypertension Pneumonia NSCLC**** NSCLC Infection Pneumonia	-	Device-related infection, rash, pneumonia. Vancomycin trough level high at 34.9 (no units).	Hypertension, chronic obstructive pulmonary disease	Chemotherapy discontinued, no improvement. Other suspects discontinued, recovered.	Ramucirumab one month prior. Infection during chemotherapy. AKI and rash after start antibiotics.
16	97/F	Enalapril, ciprofloxacin, furosemide, metamazole (all I)	- - - -	Oral Oral Oral Oral	c. 2 years 0 days - 2 days	Hypertension UTI Cardiac failure Osteoarthritis	-	Serum creatinine 501 mmol/L	CRF, hypertension	Enalapril, ciprofloxacin and metamazole discontinued, recovered	-

*LT, drug administration assumed to be long term in a report where end date recorded and precise dates for short term drugs recorded in a report;
 **UTI, urinary tract infection;
 ***T2DM, Type 2 diabetes mellitus;
 ****CRF, chronic renal failure;
 *****NSCLC, non-small cell lung cancer.

In five case reports, recent commencement of a diuretic (4, 5) or an NSAID (8) or recent rather than long term prescription of enalapril with a diuretic (11) may have triggered enalapril-related AKI or contributed when ciprofloxacin was added. One of these patients (4) and two others (2, 6) had diarrhoea and/or vomiting which may have had a similar effect. It is theoretically possible that in case report 3 renal tubular inhibition of methotrexate excretion by ciprofloxacin led to renal failure.

An important feature of the 11 reports, with the exception of reports 1 and 10, is the patient characteristics that made them vulnerable to renal failure in association with enalapril use.³ Seven patients were taking diuretics and two were taking NSAIDs, three had diarrhoea and/or vomiting and four had cardiac conditions. Five patients were aged over 80 years and it is of note that four of these very elderly patients had two or more risk factors in

addition to their age for enalapril-related renal failure. Therefore, if there is a ciprofloxacin effect when taken with enalapril, it is most evident in very vulnerable patients.

If the AKI after ciprofloxacin was introduced could be entirely explained by infection or antibiotic-related diarrhoea, then disproportionate reporting would be expected for AKI with enalapril and other antibiotics. This disproportionality ($\Omega_{025} > 0$) was not observed with amoxicillin, azithromycin or flucloxacillin which, like ciprofloxacin, are used in an ambulatory setting (Table 2). The disproportionality measures do support a class effect of ACE inhibitors with ciprofloxacin ($\Omega_{025} > 0$). More evidence is needed to ascertain if there is a class effect for fluoroquinolones as there were few reports.

Table 2. Disproportionality statistics from VigiBase for combinations of acute kidney injury with (1) ciprofloxacin and ACE inhibitors (2) enalapril and a fluoroquinolone (3) enalapril and other antibiotics

Combination no.	Drug 1	Drug 2	Drug 2 status	N observed	N expected	Ω	Ω_{025}^{***}
1	Ciprofloxacin	Enalapril	SI*	15	2	2.38	1.56
1	Ciprofloxacin	Enalapril	SIC**	61	30.7	0.93	0.55
1	Ciprofloxacin	Lisinopril	SI	10	3.8	1.30	0.27
1	Ciprofloxacin	Lisinopril	SIC	129	59.4	1.11	0.85
1	Ciprofloxacin	Ramipril	SI	13	3.2	1.88	0.99
1	Ciprofloxacin	Ramipril	SIC	82	41.0	0.99	0.66
2	Enalapril	Levofloxacin	SI	3	0.7	1.49	-0.56
2	Enalapril	Levofloxacin	SIC	31	19.9	0.63	0.08
3	Enalapril	Amoxicillin	SI	2	1.4	0.42	-2.20
3	Enalapril	Amoxicillin	SIC	21	15.2	0.45	-0.23
3	Enalapril	Azithromycin****	SIC	11	6.9	0.65	-0.33
3	Enalapril	Flucloxacillin****	SIC	3	6.6	-1.01	-

*suspected or interacting;
 **suspected, interacting or concomitant;
 *** $\Omega_{025} > 0$, disproportionate reporting suggesting a drug-drug interaction;
 ****insufficient reports for suspected and interacting (SI) only.

Literature and Labelling

The United Kingdom summary of product characteristics and US Food and Drug Administration (FDA) labels for enalapril (Innovace®, Vasotec®) and ciprofloxacin (Cipro®) do not list the two substances as interacting.^{3,6,7,8} These labels reiterate the information about renal dysfunction with each of these medicines, described in the Introduction.

Lomaestro² conducted a literature review to ascertain the incidence and characteristics of fluoroquinolone-related nephrotoxicity. Publications were mostly case reports and the incidence was difficult to estimate. Nearly all of the 44 reports of acute renal failure identified involved patients aged over 50 years. The most frequently reported pathology was acute interstitial nephritis. A high proportion of patients were taking other nephrotoxic medicines, particularly chemotherapeutic and immunosuppressive agents. One patient was taking an ACE inhibitor.

A nested case-control study examined the risk of AKI with the use of fluoroquinolones in a cohort of men aged between 40 and 85 years in the US IMS Lifelink Health Plan Claims Database.¹ The number of cases and controls was 1,292 and 12,651 respectively. After adjusting for fluoroquinolone indication, which included genitourinary infections, diseases associated with AKI including congestive heart failure and diabetes, and potentially nephrotoxic medicines with high use i.e. NSAIDs, loop diuretics and renin-angiotensin blockers, the rate ratio (RR) of AKI with current fluoroquinolone use was 2.18 (95% confidence interval (CI) 1.74 – 2.73), which equated to an absolute increase in AKI of 6.5/10,000 person-years or one additional case per 1,529 patients given a fluoroquinolone. This finding was supported by the results of a case-time-control analysis in the same cohort in which within-patient comparisons were made of drug exposures.

The findings were similar whether or not patients had genitourinary infection or chronic kidney disease. The highest RR for the individual fluoroquinolones was for ciprofloxacin (2.76, 95% CI 2.03 – 3.76). This increased risk was not found with amoxicillin and azithromycin suggesting infection was not an alternative explanation.

The authors also hypothesised interactions between fluoroquinolones and NSAIDs, loop diuretics or renin-angiotensin system blockers (ACE inhibitors or angiotensin-receptor blockers) but only had sufficient power to examine the renin-angiotensin system blockers. There was no increase in risk of AKI with renin-angiotensin system blocker treatment alone (RR 1.00, 95% CI 0.84 – 1.18) but the combined use of these medicines with fluoroquinolones increased the RR for AKI from 2.18 for fluoroquinolones alone to 4.46 (95% CI 2.84 – 6.99) which was greater than the additive risk.

The lack of increased risk of AKI with renin-angiotensin system blockers alone was unexpected. The authors considered that physician monitoring of

serum creatinine levels, particularly after starting renin-angiotensin blockers may be one explanation.

Discussion and Conclusion

The VigiBase case reports describe AKI occurring soon after ciprofloxacin was prescribed in patients taking enalapril. This adverse effect could be attributable to ciprofloxacin alone or to infection. However, three observations suggest a combined effect. Firstly, the increased disproportionality measure ($\Omega_{025} > 0$) for the enalapril/ciprofloxacin/AKI combination compared with the background data in VigiBase. Secondly, an independent nested case control study showed a greater than additive risk of AKI with co-prescribed fluoroquinolones and renin angiotensin blockers.¹ Thirdly, in the VigiBase reports a high proportion of patients were at risk of AKI including ACE inhibitor adverse renal effects, but AKI did not occur until ciprofloxacin was added.

While the contributing reports to the other combinations in Table 2 need more clinical assessment, the disproportionality measures suggest that infection and antibiotic-related diarrhoea do not completely explain the observations. In addition, the case-control study¹ suggested that urinary tract infection indications for ciprofloxacin were also unlikely to be an explanation. The disproportionality estimates in Table 2 do support a class effect of ACE inhibitors with ciprofloxacin.

A potential mechanism for the observed interaction has not been identified. Most of the published reports summarised by Lomaestro indicate acute interstitial nephritis as the underlying cause of AKI with fluoroquinolones.² This is rare although the estimated incidence of 1 in 1,526 in the case control study of hospital admissions is likely to be an underestimate as patients may have been admitted with an alternative primary diagnosis or recovered before needing admission. Interstitial nephritis or other pathology due to a fluoroquinolone could be a trigger for ACE inhibitor-related AKI or more severe AKI leading to admission. There were no pathological descriptions in the VigiBase reports.

The case control study included only men as it was nested in a cohort study of the health of men aged 40 to 85 years.¹ The VigiBase case series included both males and females and the age range was similar or older. It included patients with risk factors for acute renal failure and risk factors for ACE inhibitor-related renal failure. It could be argued that these are sufficient in themselves to explain the AKI, but the addition of ciprofloxacin just prior to onset of AKI suggests that it may have had a causal or contributory role. Also the increased risks of

AKI for fluoroquinolones with and without renin angiotensin blockers in the case-control study were estimated after adjusting for many of these risk factors.

At least half of the patients in the VigiBase series received ciprofloxacin together with enalapril in an ambulatory setting. This is also likely in the case-control study as the case patients were those admitted because of AKI. Therefore, co-prescription of enalapril and ciprofloxacin may not be uncommon in primary care. The US FDA has recently issued advice against using ciprofloxacin for specified urinary and respiratory infections, unless there are no alternatives, because of serious non-renal toxicities.⁷ The observations in the VigiBase reports and case-control study¹ therefore need further investigation to ascertain if it is advisable to extend the advice to ciprofloxacin use with an ACE inhibitor because of an additional risk of nephrotoxicity in vulnerable patients.

The VigiBase reports also provide insights into the prescribing of ACE inhibitors and reiterate the need for careful consideration of age, renal function, hydration status and concomitant prescribing of diuretics or NSAIDs, and for monitoring throughout treatment for changes in clinical status that might increase the risk of renal impairment.

References

1. Bird ST, Etmnan M, Brophy JM, Hartzema AG, Delaney JAC. Risk of acute kidney injury associated with the use of fluoroquinolones. *CMAJ* 2013;185: E475-E482.
2. Lomaestro BM. Fluoroquinolone-induced renal failure. *Drug Saf.* 2000;22:479-85.
3. Electronic Medicines Compendium: Summary of Product Characteristics for enalapril (Innovace®). Available from: <https://www.medicines.org.uk/emc/medicine/1180>. Accessed: 19 September 2016.
4. Drug consult: ACE inhibitor induced renal failure. Micromedex® Healthcare Series. [Online] Greenwood Village (Co): Thomson Micromedex. Available from: <http://www.micromedexsolutions.com>. Accessed: 21 November 2016.
5. Norén GN, Sundberg R, Bate A, Edwards IR. A statistical methodology for drug-drug interaction surveillance. *Stat Med.* 2008 Jul 20;27(16):3057-70.
6. US Food and Drug Administration: Product label for enalapril (Vasotec®). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018998s080lbl.pdf. Accessed: 26 January 2017.
7. Electronic Medicines Compendium. Summary of Product Characteristics for ciprofloxacin. Available from: <https://www.medicines.org.uk/emc/medicine/32450>. Accessed: 19 September 2016.
8. US Food and Drug Administration: Product label for ciprofloxacin (Cipro®). Available from: http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019537s085_020780s042lbl.pdf. Accessed: 26 January 2017.

Ivermectin and serious neurological events

Dr Rebecca E Chandler, Uppsala Monitoring Centre

Summary

Ivermectin is an anti-parasitic agent. It is indicated for use in the treatment of strongyloidiasis (*Strongyloides stercoralis*) and onchocerciasis (*Onchocerca volvulus*), but is also commonly used to treat scabies. Ivermectin is thought not to cross the blood-brain barrier in humans as it is excluded by a P-glycoprotein drug pump (mdr-1). Therefore, it has been considered to be free of the potential to cause neurological adverse drug reactions, except in situations of overdose. Serious neurological adverse events (SNAEs) were initially reported in public health programs in Africa to eliminate onchocerciasis through community-based ivermectin treatment. Cases of encephalopathy and coma were reported in Cameroon and the Democratic Republic of Congo in persons who concomitantly harbored high densities of another

filarial species, *Loa loa*. Subsequent analyses revealed a correlation between pre-ivermectin treatment *Loa* microfilarial density and the risk of developing an SNAE. In VigiBase, the WHO global database of individual case safety reports, a report describing a case of encephalopathy with ivermectin from the Democratic Republic of Congo, which reported a lack of evidence of concomitant loiasis, triggered a review of the database. This led to the identification of a case series of SNAEs occurring with the use of ivermectin outside the onchocerciasis indication. The occurrence of an SNAE after ivermectin may therefore not be entirely explained by concomitant onchocerciasis or loiasis infections. Knowledge of potential drug interactions and exploration

of individual variations in the *mdr-1* gene may be warranted to ensure safer use of ivermectin.

Introduction

Ivermectin is a member of the class of avermectins, which are highly active broad-spectrum, anti-parasitic agents. It is indicated for use in the treatment of strongyloidiasis (*Strongyloides stercoralis*) and onchocerciasis (*Onchocerca volvulus*); however, it is also commonly used to treat scabies, in circumstances such as immunocompromised patients, when topical therapy has failed, or institutionalized patients.^{1,2} Ivermectin is not thought to readily cross the blood-brain barrier in humans, as it is excluded by a P-glycoprotein drug pump (*mdr-1*). Therefore, it has been considered to be free of the potential to cause neurological adverse drug reactions, except in situations of overdose.³

Serious neurological adverse events (SNAEs) were initially reported in public health programs in Africa to eliminate onchocerciasis through community-based ivermectin treatment; cases of encephalopathy and coma were reported in Cameroon and the Democratic Republic of Congo in persons who concomitantly harbored high densities of another filarial species, *Loa loa*. Subsequent analyses revealed a correlation between pre-ivermectin treatment *Loa loa* microfilarial density and the risk of developing an SNAE.^{4,5}

In September 2015, a signal detection screening of VigiBase, the WHO global database of individual case safety reports, was performed focussing on drug-event combinations sensitive to reporting patterns mainly in Africa, Asia and Latin America and the Caribbean. During this screening a report for an SNAE (ataxia) from the Democratic Republic of the Congo was identified, which stated "This patient of 56-year old realises these conditions [encephalopathy]. It is very surprising to notice that there was no microfilariae in the calibrated thick blood smear." The lack of evidence of a high density of *L. loa* appeared to challenge the literature on SNAEs with ivermectin, and therefore it triggered a review of all SNAEs beyond the indication of use for onchocerciasis which could not be explained by concomitant infection with *L. loa*.

Reports in VigiBase

All reports for ivermectin received into VigiBase up to 27 November 2016 were identified for investigation. A total of 1,668 reports for ivermectin were identified. The most commonly reported adverse events (AEs) for ivermectin were pruritus (25.3%), headache (13.9%) and dizziness (7.5%).

Under the MedDRA System Organ Class "Neurological disorders" 426 reports were classified, and 156 of these were classified as "serious" according to ICH Guidance.⁶ Of the serious reports, 60.9% (95) of them originated from Africa, 20.5%

(32) from the Americas, 12.2% (19) from Europe, and 6.4% (10) from Asia. One duplicate report was identified and excluded from the analysis.

Sixty-four of the 155 serious reports described the use of ivermectin for *O. volvulus*. Forty-two did not include an indication; one reported only "infection parasitic". After clinical analysis, nineteen reports were excluded from this analysis: the reasons for exclusion were neurological AEs reported in the context of other clinical syndromes (lactic acidosis/circulatory collapse, cerebral infarction/cerebral artery embolism, neuroleptic malignant syndrome, hepatitis/hepatic failure, brain cancer, pneumonia with hypotension, accidental exposure to product, sepsis complicating chemotherapy, multi-organ failure, history of epilepsy, Alzheimer's disease), topical ivermectin for rosacea, prolonged time to onset of ivermectin (8 years), and unclear onset of symptoms in relation to ivermectin.

The remaining 29 reports are included in this case series and were received from, Canada, France, Germany, Japan, the Netherlands, Sierra Leone, and the United States. The patient ages were mentioned in 25 reports and ranged from 11 to 97 years. Fifteen described males, 13 described females and the gender was not provided in one report.

Scabies was included as an indication in eleven reports, acarodermatitis in eight, filariasis due to *Wucheria bancrofti* in five, strongyloidiasis in three, taeniasis in one and myiasis in one. The time to onset of the SNAEs ranged from hours to 14 days, with 14 cases noting a time to onset of one day or less.

As seen in Table 1, examples of serious ADRs reported include unable to walk, consciousness disturbed or depressed level of consciousness or loss of consciousness, seizure or convulsion, encephalopathy or coma, and tremor.

The dosages of ivermectin ranged between 3 mg and 24 mg. Most of the cases reported a one-time dose or two doses separated by one week. Weight information was provided for the majority of cases, and there was no suggestion of overdose based on the data provided.

Nine reports documented a positive dechallenge, with resolution of symptoms after discontinuing ivermectin. One documented a positive rechallenge, with recurrence of symptoms with re-exposure on two occasions. Two patients died.

One case has been previously published, and documented the presence of ivermectin in brain tissue: "A 64-year-old male with a past medical history of giant cell arteritis, treated with prednisone developed sepsis, complicated by multisystem organ failure, after an aortic valve replacement. Sputum culture revealed *S.*

stercoralis. A diagnosis of *S. stercoralis* hyperinfection syndrome was made; he was initiated on ivermectin 12 mg every 48 hours. He received three oral doses followed by two subcutaneous doses. In spite of clinical and microbiological improvement, the patient remained in a vegetative state and died on day 25. Autopsy revealed an elevated level of ivermectin in the brain tissue, 14 days after the last dose.”⁷

Literature and Labelling

The neurological events of dizziness (2.8%), somnolence (0.9%), vertigo (0.9%), and tremor (0.9%) were observed in human clinical trials for the treatment of strongyloidiasis, while drug-related headache (0.2%) was observed in trials for onchocerciasis; these events are included in the product label. Also included in the labelling is a warning for overdose which can manifest with headache, dizziness, asthenia, seizure, ataxia, and paresthesia.¹

The label for ivermectin also provides the following warning: “Rarely, patients with onchocerciasis who are also heavily infected with *Loa loa* may develop a serious or even fatal encephalopathy either spontaneously or following treatment with an effective microfilaricide. In these patients, the following adverse experiences have also been reported: pain (including neck and back pain), red eye, conjunctival hemorrhage, dyspnea, urinary and/or fecal incontinence, difficulty in standing/walking, mental status changes, confusion, lethargy, stupor, seizures, or coma. This syndrome has been seen very rarely following the use of ivermectin. In individuals who warrant treatment with ivermectin for any reason and have had significant exposure to *Loa loa*-endemic areas of West or Central Africa, pre-treatment assessment for loiasis and careful post-treatment follow-up should be implemented.”¹

Discussion and Conclusion

This case series describes SNAEs with the use of ivermectin beyond its indication for *O. volvulus*. Ivermectin acts by binding to glutamate-gated chloride ion channels which occur in invertebrate nerve and muscle cells; an increase in the permeability of the cell membrane results in paralysis and death of the parasite. It can also bind to mammalian GABA receptors and GABA-gated ion channels; however, neurotoxicity is prevented by the action of the P-glycoprotein drug pump (mdr-1) which limits penetration of the blood-brain barrier within the allowable dosage ranges for humans.³

It is well established in the veterinary world that certain breeds of dogs, such as collies, are sensitive to the neurotoxic effects of ivermectin; a loss of function in the mdr-1 gene in these breeds allows for an accumulation of ivermectin within the brain.⁸

Symptoms of neurotoxicity include lethargy, drooling, tremors/seizures, inability to stand, disorientation, coma.

Our data suggest that individuals may experience SNAEs outside the contexts of overdose and *L. loa* co-infection. While a number of AEs experienced by subjects in this case series are included in the product label (dizziness, headache, tremor), there were many other events which are similar to those described as neurotoxic effects as found in overdose or in susceptible dogs: coma, loss of consciousness/depressed level of consciousness, abasia and coma.

A number of cases included in the case series may be related to concomitantly administered drugs. Drugs that are substrates of CYP3A4 enzymes are often also substrates for P-glycoprotein transport, and thus there may be a risk of increased absorption past the blood-brain barrier with concomitant administration.⁹ Several cases presented here reported concomitant use of such drugs, such as statins, HIV protease inhibitors, calcium channel blockers, and benzodiazepines. Current labelling for ivermectin contains no warning for co-administration with CYP3A4 substrates.

Another possible explanation is that some humans experiencing an SNAE after ivermectin therapy may also have mutations in the mdr-1 gene, allowing for penetration of ivermectin into the central nervous system. More than 50 naturally occurring single nucleotide polymorphisms (SNP) have been identified in the mdr-1 gene; the majority of these SNP are silent, and there is no current evidence of a mutation that results in loss of function. However, various combinations of these SNP, comprising different P-glycoprotein haplotypes, have been found to exhibit reduced mdr-1 expression.¹⁰ Bourguinat *et al* performed a study in which they analysed mdr-1 genotypes in 13 subjects from Cameroon: four who experienced a serious adverse event and nine who did not. Haplotypes associated with altered drug disposition were present as homozygotes in two of the serious AE patients and in none of the control patients.¹¹ One of the cases in our series was investigated for the most common polymorphisms associated with decreased mdr-1 expression and found that none were present; however, further details were not provided.⁸

In conclusion, there is evidence that SNAEs can occur with ivermectin beyond the treatment of *O. volvulus* complicated by concomitant *L. loa* infection. Potential explanations include concomitantly administered drugs which inhibit CYP3A4 and polymorphisms in the mdr-1 gene.

Table 1. Case series describing serious neurological adverse events after treatment with ivermectin beyond the onchocerciasis indication

Case	Age/Sex	Indication	Dose	Weight (kg)	Other suspect or concomitant medications	Reported terms	Time to onset	Additional info
1	18/M	Scabies infestation	15mg, one dose	79	-	Lightheadedness, headache, unable to walk	1 day	Recovered in 24 hours Positive dechallenge
2	58/F	Acarodermatitis	12 mg, 1 per 1 day	60	Alprazolam, etizolam (both C)	Consciousness disturbed	0 days	Positive dechallenge
3	-/F	Myiasis	12 mg, 1 per 1 day	-	-	Seizure, off label use	-	Not recovered
4	51/M	Acarodermatitis	18 mg, 2 doses separated by one week	79	Pregabalin, lamotrigine, ariprazole, meloxicam, simvastatin, docusate (all C)	Abasia, aphasia, blindness, disease recurrence	-	Positive rechallenge
5	54/F	Acarodermatitis	-, 2 tablets, 2 doses separated by one week	68	-	Convulsion, local swelling, nausea, headache, heart rate increased, confusional state	-	-
6	32/F	Scabies	24mg, one dose	109	-	Tremor, dizzy spells, mucosal dryness, abdominal pain lower	8 hours	-
7	81/F	Acarodermatitis	12 mg, 2 doses separated by one week	-	Digoxin, rebamipide, crotamiton, magnesium oxide, senna (all C)	Depressed level of consciousness, vomiting, asphyxia, pruritis aggravated, skin eruption	5 days after last dose	Died, 5 days after last dose from the events of depressed level of consciousness and asphyxia. Digoxin initiated 1 day prior to death.
8	11/F	Scabies	9 mg, one dose	40	-	Encephalopathy, coma, emesis	1 day	Recovered Positive dechallenge LP, EEG and MRI all performed
9	13/M	Scabies	1 DF*, 1 per 1 day	-	Piperonyl butoxide/esdepallethrine (topical) (S)	Dizziness, crying, abnormal, monoparesis, tremor, rigors, chills	10 hours	Recovered Positive dechallenge
10	47/F	Scabies	9 mg, 2 doses separated by one week	68	Piperonyl butoxide/esdepallethrine (topical) (S)	Muscle weakness, hypoaesthesia, paraesthesia	7 days	Recovered
11	28/M	Scabies	18mg, one dose	-	-	Confusional state, amnesia, malaise, emesis	1 day	Recovered; Similar symptoms reports twice in the past after ivermectin
12	68/M	Scabies	18mg, one dose	-	-	Confusional state, disorder convulsive	14 days	Not recovered
13	33/M	Scabies	12mg, one dose	65	Darunavir, ritonavir (both S)	Convulsions generalised	1 day	Recovered Positive dechallenge with all 3 drugs. Patient had started darunavir 12 months prior and ritonavir 8 days prior.
14	81/M	Scabies	3 mg, one dose on two days	-	-	Cerebellar syndrome, mental confusion, MRI abnormal	2 days	Drug withdrawn, no effect observed MRI abnormal 2 weeks after dosing
15	64/M	Strongyloidiasis	12 mg oral, then subcutaneous	57	-	Coma, neurotoxicity	-	Drug withdrawn, fatal outcome Therapy initiated for Strongyloides stercoralis infection in patient on prednisone for giant cell arteritis. Patient was s/p aortic valve replacement. Ivermectin levels measured in brain tissue at autopsy (30 ng/g). None of the most common polymorphisms in mdr-1 present
16	81/M	Acarodermatitis	9 mg, one dose	50	Rivastigmine, memantine, lornoxicam, troxipide (all C)	Tremor, pyrexia	0 days	Positive dechallenge

SIGNAL

Case	Age/Sex	Indication	Dose	Weight (kg)	Other suspect or concomitant medications	Reported terms	Time to onset	Additional info
17	59/F	Strongyloidiasis Nematodiasis	21 mg, one dose on 2 days	100	Levothyroxine, olopatadine, vitamins, omega-3, melatonin, ascorbic acid, formoterol/budesonide, doxycycline, potassium citrate, pioglitazone, probiotics, vitamin D, prasterone, progesterone, colesevelam, montelukast, desvenlafaxine (all C)	Pain in jaw, tremor, chest pain, chills, back pain, tachycardia, dyspnoea, loss of consciousness, pain in extremity, thinking abnormal, peripheral coldness, hypersomnia, dizziness, asthenia, feeling abnormal, palpitations, paraesthesia, fatigue, blood potassium decreased, dysgeusia, constipation, muscle twitching, sedation, vertigo, sensation of heaviness, feeling cold, mood altered, feeling drunk, oropharyngeal pain, coxsackie virus test positive, inappropriate schedule of drug administration, orthostatic hypotension, neuralgia, affect lability, hypertension, asthma, confusional state, cough, nystagmus, headache, pyrexia, somnolence	1-2 days	Drug withdrawn, no effect observed
18	-/-	Acarodermatitis	-	-	Valproic acid, levetiracetam (both C)	Seizure, off label use	-	-
19	24/M	Scabies	3 mg, one dose	-	Oxatamide (S)	Confusion, convulsive disorder, cephalgia, fatigue, fall	0 days	Hospitalised, recovered
20	75/F	Taeniasis	6 mg	59	Lisinopril, amlodipine, metoprolol, clopidogrel (all C)	Asthenia, dizziness, dyspnoea, paraesthesia, vision decreased	0 days	Recovered with sequelae
21	-/M	Scabies infestation	12 mg	70	Ranitidine, amantidine, trazadone, lorazepam, haloperidol, topirimate, hydroxyzine, risperidone (all C)	Confusional state, unconsciousness	-	Hospitalised
22	-/M	Strongyloidiasis	18 mg, one dose on 2 days	86	-	Quality of life decreased, sleep disorder	-	-
23	56/F	Acarodermatitis	12 mg, one dose	55	Terbinafine (S) Dexamisoprazole, milnacipran, gabapentin, promethazine, meloxicam, trazadone, levothyroxine, propranolol, Lisinopril, predinose, azathioprine, diazepam, norriptyline, lansoprazole, amoxicillin, furosemide, hydrochloroquine, vitamin D, vitamins (all C)	Aphasia, somatic delusion, abnormal faeces, alopecia, dry mouth, dyspnoea, ear infection, flushing, gastrointestinal motility disorder, headache, heart rate increased, lip swelling, musculoskeletal discomfort, oral discomfort, red blood cell count decreased, swollen tongue, urine colour abnormal, urine odour abnormal, weight decreased, white blood cell count decreased	2-5 days for aphasia and somatic delusion	Drug withdrawn, no effect observed
24	36/M	Filariasis due to Wuchereria bancrofti	12 mg, one dose	-	Albendazole (S)	Headache, vomiting, diarrhoea, abdominal discomfort	1 day	Recovered
25	43/F	Filariasis due to Wuchereria bancrofti	9 mg, one dose	-	Albendazole (S)	Headache, dizziness, vomiting	2 days	Recovered
26	11/F	Filariasis due to Wuchereria bancrofti	9 mg, one dose	-	Albendazole (S)	Headache, dizziness, vomiting	0 days	Recovered
27	28/M	Filariasis due to Wuchereria bancrofti	12 mg, one dose	-	Albendazole (S) Diclofenac, amoxicillin (both C)	Unconsciousness	0 days	Recovered Hospitalised 4 hours, gastric lavage
28	72/M	Filariasis due to Wuchereria bancrofti	12 mg, one dose	-	Albendazole (S)	Headache, abdominal discomfort, itching, vomiting, oedema	0 days	Recovered
29	97/F	Acarodermatitis	9 mg, 2 doses separated by one week	47	Febuxostat, furosemide, lansoprazole, sennoside a+b, magnesium oxide, carbocisteine, etizolam (all C)	Depressed level of consciousness, loss of consciousness, vomiting	6 days after 1st dose and 5 days after 2nd dose	Recovered Positive dechallenge

*DF = Dosage form

References

1. DailyMed: Product label for ivermectin (Stromectol®). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=681888c9-af79-4b7d-ae80-c3f4f6f1effd>. Accessed: November 2016.
2. Fawcett RS. Ivermectin use in scabies. *Am Fam Physician*. 2003;68(6):1089-92.
3. Schinkel AH, Smit JJM, van Tellingen O, Beijnen JH, Wagenaar E, van Deemter L et al. Disruption of the mouse *mdr1a*-p-glycoprotein gene leads to a deficiency in the blood- brain barrier and to increased sensitivity to drugs. *Cell* 1994;77:491-502.
4. Boussinesq M, Gardon J, Gardon-Wendel N, Chippaw JP. Clinical picture, epidemiology, and outcome of Loa-associated serious adverse events related to mass ivermectin treatment of onchocerciasis in Cameroon. *Filaria J*. 2003; (Suppl 1): S4.
5. Gardon J, Gardon-Wendel N, Demanga-Ngangue Kamguo J, Chippaux JP, Boussinesq M. Serious reactions after mass treatment of onchocerciasis with ivermectin in an area endemic for Loa loa infections. *Lancet* 1997;350:18-22.
6. ICH Expert Working Group. Post-approval safety data management: definitions and standards for expedited reporting. 2003. Available from: https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E2D/Step4/E2D_Guideline.pdf. Accessed: November 2016.
7. van Westerloo DJ, Landman GW, Prichard R, Lespine A, Visser LG. Persistent coma in Strongyloides hyperinfection syndrome associated with persistently increased ivermectin levels. *Clin Infect Dis*. 2014;58(1):143-4.
8. Mealey, KL, Bentjen SA, Gay JM, Cantor GH. Ivermectin sensitivity in collies is associated with a deletion mutation of the *mdr1* gene. *Pharmacogenetics*. 2001;11:727-33.
9. Benet LZ, Cummins CL, Wu CY. Unmasking the dynamic interplay between efflux transporters and metabolic enzymes. *Int J Pharm*. 2004;277(1-2):3-9.
10. Macdonald N, Gledhill A. Potential impact of ABCB1 (p-glycoprotein) polymorphisms on avermectin toxicity in humans. *Arch Toxicol*. 2007;81:553.
11. Bourguinat C, Kamgno J, Boussinesq M, MacKenzie CD, Prichard R, Geary TG. Analysis of the *mdr-1* gene in patients co-infected with *Onchocerca volvulus* and Loa loa who experienced a post-ivermectin serious adverse event. *Am J Trop Med Hyg*. 2010;83(1):28-32.

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.

Uppsala Monitoring Centre (UMC) Tel: +46-18-65 60 60, E-mail: info@who-umc.org	Box 1051, SE-751 40 Uppsala, Sweden www.who-umc.org
---	---

Recommendations from the 40th 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 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 direction of future PV activities. Recommendations are made by delegates through group work. The fortieth annual meeting of representatives of NPCs participating in the WHO PIDM was held from 7 to 10 November 2017, in Kampala, Uganda. 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 countries' 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: Pharmacovigilance inspection: needs, capacity and cooperation

Working group moderators: Mick Foy, Medicines and Healthcare products Regulatory Agency (MHRA); MHRA and Christabel Khaemba, Pharmacy and Poisons Board, Kenya

Rapporteur: Deliana Aboka, WHO Collaborating Centre for International Drug Monitoring



The objective of the working group was to discuss industry obligations, regulatory oversight, country experiences, and opportunities for learning and work-sharing for pharmacovigilance (PV) inspections. Participants from 24 countries attended the working group. Of these, two countries were actively conducting PV inspections. Best practices and lessons learnt were shared. Resources available to countries for inspections were discussed. Although most countries in the group have not yet conducted a PV inspection, it was agreed that not all need to, as work can be shared, for example in South East Asia there is an established governmental network and it may not be necessary for all countries to do all inspections.

Recommendations from working group one: Pharmacovigilance inspection: needs, capacity and cooperation

For National Pharmacovigilance Centres

- To identify if regional inspections amongst neighbouring countries can be conducted, particularly for resource limited countries.
- To include PV in regulation and enforce legislation. The law should require that Marketing Authorisation Holders (MAH)s have risk minimization plans as part of their dossiers and that MAH licenses should be issued after a risk minimization plan is in place.
- To apply strategy-based inspections and focus on new medicinal products rather than generics.
- To leverage available resources and give feedback to Contract Research Organization (CROs) and MAH when inspections are conducted.
- To take a collaborative approach to inspections. Roles and responsibilities of stakeholders (companies, health care professionals, drug regulator) should be defined.
- To use WHO indicators to measure PV processes.

For WHO and WHO Collaborating Centres

- To support capacity strengthening in Member States for PV inspections.
- To promote the sharing and exchange of information and resource materials for PV inspections, and leverage existing regulatory networks in Member States for capacity building, at regional, national and global levels.
- To create a platform where all Member States can share communication materials, check-lists and guidelines.
- To share all pharmacovigilance guidelines and tools with all Member States (e.g. tools used for medication error).
- To support countries with PV training and to promote a network to form collaborations, specifically between the NPCs and Qualified Person for Pharmacovigilance (QPPV) in MAHs, for example organising a workshop that brings them together.

Working group two: Risk Management Plans (RMPs) for teratogenic drugs

Moderators: Rachida Soulaymani, Centre Antipoison et de pharmacovigilance du maroc, Morocco; and Helen Ndagije, National Drug Authority, Uganda

Rapporteur: Annette Takaendesa, Medicines Control Authority of Zimbabwe



The objective of the workshop was to review challenges in implementing risk management plans (RMPs) for teratogenic medicines. Representatives from 12 countries (Belgium, Brazil, Ethiopia, Kenya, Mozambique, Morocco Namibia, Oman, South Africa, Togo, Uganda, and Zimbabwe) attended the session. The group looked at specific examples of challenges in implementing RMPs for teratogenic medicines and proposed ways in which challenges could be addressed. Issues discussed included: provision on medicines without a prescription; lack of information given to patients on teratogenic medicines when prescribing; lack of public awareness of teratogenicity; lack of involvement of NPCs in the review of RMPs; lack of implementations of RMPs; and lack of

specialists in the use of medicines in pregnancy. Most NPCs need support with monitoring safety of medicines in pregnancy and there is limited information on medicine usage during pregnancy.

Recommendations from working group two: Risk Management Plans (RMPs) for teratogenic drugs

For National Pharmacovigilance Centres

- To get involved in reviewing the RMPs submitted by the Marketing Authorization Holders (MAH) during registration or licensing of a product; this involves actively supervising RMP implementation and routinely ensuring information is updated throughout the lifetime of the product.
- To have a list of teratogenic medicines in PVCs
- To promote awareness of teratogenic medicines to healthcare providers through training and patient sensitization, targeting women of child bearing age.
- To obtain a PV tool-kit on use of medicines during pregnancy.
- To be able to detect signals for medicines used in pregnancy and have a plan on how to manage these signals.
- To collaborate with existing birth-defects monitoring authorities such as the neonatology departments, or the teratology information centres which deal with monitoring abnormalities in neonates.

Introduce relevant regulations to:

- prevent pharmacists from providing certain medicines (prescription and teratogenic medicines) without a prescription;
- ensure the 'caution in use' section of package inserts and patient information leaflets for teratogenic products is highlighted and prominent (pictograms can also be used to illustrate the message to patients);
- ensure pharmacists routinely check if a medicine is teratogenic and communicate potential teratogens to prescribers;
- make sure prescribers communicate to patients the risks involved in taking teratogenic medicines; and
- to provide information to patients and prescribers about medicines and risks involved when a teratogenic medicine is taken.

For WHO and WHO Collaborating Centres

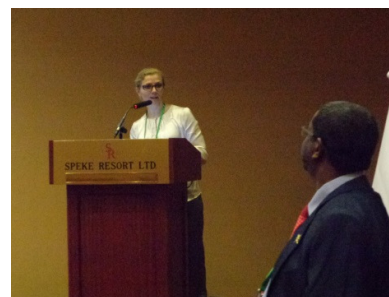
- To support NPCs to enhance competencies.
- To develop and update a guidance document highlighting key issues on known teratogenic medicines.
- To develop a pregnancy tool-kit and provide a platform for countries to share experiences and a list of teratogenic medicines. The toolkit should include: causality assessments, setting up a pregnancy registry, guidance on sources of information for teratogenic medicines, methods for collecting information (e.g. reporting forms for medicines used during pregnancy).
- To organize a signal sprint for medicines used during pregnancy and investigate tools that can identify potential safety risks in medicines that are not yet known to be teratogenic.

Working group three: Scope of pharmacovigilance

Moderators: Hussain Al Ramimmy, Ministry of Health, Oman; and Mona Vestergaard Laursen, Danish Medicines Agency, Denmark

Rapporteur: Peter Babigumira Ahabwe, Uganda

The objective of the working group was to discuss current developments in PV, its evolving remit and scope for other medicinal products (e.g. diagnostics and devices, veterinary medicines). Representatives from 12 Member States participated in the working group (Barbados, Brazil, Canada, China, Croatia, Denmark, Iraq, Kenya, Oman, Singapore, Uganda, Zambia). Pharmacovigilance concepts and tools can be applied to areas in healthcare other than medicines and vaccines and many PV departments already manage reports related to: medical devices, medication errors (both ADRs and near misses), traditional and plant medicines, biologicals and biosimilars, illicit drugs, falsified and counterfeit products, cannabis and other recreational drugs, chemicals and poisoning, abuse and overdose. One of the major challenges discussed was managing reports received by NPCs for products other than medicines and vaccines. Different departments within national medicines agencies and between different agencies (other than medicines) may diverge and responsibilities of NPC towards reports received related to products other than vaccines and medicines are not clear. Broadening the scope of PV requires additional resources, irrespective of the region.



Recommendations from working group three: Scope of Pharmacovigilance

For National Pharmacovigilance Centres

- Perform a stakeholder/network mapping exercise to provide an overview of definitions, rules, guidelines, and legal frameworks in different areas relevant to pharmacovigilance.
- Encourage and emphasize work and information sharing with other relevant departments and agencies.

For WHO and WHO Collaborating Centres

- To promote the application of PV to areas other than medicines and vaccines, by collating and summarizing experiences on collection, management, sharing reports and communicate risks to healthcare professionals and patients.
- To support the formation of a policy on polypharmacy practices. Polypharmacy practised by health workers, self-medication by patients and self-prescription of opioids are an increasing concern and compromises patient safety.
- To form guidelines on quality issues. Currently this is difficult to manage as there are different guidelines and overlapping responsibilities.

- To collect information on cost of ADR.
- To develop an overview of the “practical implications” of broadening the scope of pharmacovigilance for all pharmacovigilance stakeholders. Current tools, guidelines and methodologies should be modified to support the work of NPCs to broaden PV. This includes additional data sources and activities beyond the collection of ADR reports.
- To investigate/ explore the possibility of centres sending reports of safety issues/harmful effects of products other than drugs or vaccines to VigiBase (or a patient safety database) with the purpose of collecting and sharing knowledge and tools, including signal detection tools for these reports.

For all stakeholders

- All stakeholders should apply the PV ‘principles’ and tools to collect and manage reports on safety issues/harmful effects of products beyond medicines and vaccines for overall patient safety.
- The PV community should take the opportunity to apply PV principles and tools with available resources.

Working group four: Risk Minimization: Roles, Responsibilities and Implementation

Moderators: Juan Roldán Saelzer, Instituto de Salud Publica, Chile; and Maia Uusküla, State Agency of Emdicines, Estonia

Rapporteur: Djamila Reis, Agencia de REgulacao e Supervisao dos Produtos Farmaceuticos e ALimentares, ARFA, Cabo Verde; and Manal Younus, Iraq PV Centre, Iraq

Representatives from 20 countries (Burkina Faso, Cape Verde, Chile, Croatia, Democratic Republic of Congo (DRP), Egypt, Estonia, Ghana, India, Iraq, Japan, Malawi, Mali, Morocco, Namibia, Norway, Singapore, Sri Lanka, Thailand and Uganda) participated in this working group. The group reviewed current legislations, and risk minimization practices and discussed what role industry should play in forming and implementing RMPs. Usually a global RMP is submitted without adaption to local needs of low and middle income countries. It was agreed that a qualified PV lead is critical, RMPs should be made a legal requirement, and national drug authorities should request studies to be carried out. The group also identified various risk minimization activities such as translation of leaflets and labels into national languages, information campaigns to health care professionals and the general population, restrictions on prescribing, analyses of consumption, teratogenic medicines. Work-sharing and opportunities for collaboration were identified.



Recommendations from working group four: Risk Minimization: Roles, Responsibilities and Implementation

For WHO and WHO Collaborating Centres

- To provide technical support and platforms to exchange information and promote collaborative initiatives.
- To help Member States strengthen assessment of gaps and avoid duplication of assessments.
- To support training centres and twinning programs.
- To form general RMP and specific guidelines for products that are used only in specific geographic areas.

Working group five: How do we measure the impact of pharmacovigilance?

Moderators: Djamila Reis, Agencia de Regulacao e Supervisao dos Produtos Farmaceuticos e Alimentares, ARFA, Cabo Verde; and Sigurd Hortemo Norwegian Medicines Agency (NOMA), Norway Rapporteur: Deliana Aboka, WHO Collaborating Centre for International Drug Monitoring

Representatives from 13 countries participated in the session. Only a few had conducted an impact assessment. The group reviewed the challenges and surrogate measures for investigating the impact of PV. Challenges included: different interpretations and confusion of outputs and inputs of assessments with outcomes; requests for monetary compensation with PV impact assessments; and lack of planning tools to measure impact. Methods of measuring impact were shared. The use of surveys was one method. Another was the use of a medicines registry to assess impact of a safety communication.



Recommendations from working group five: How do we measure the impact of pharmacovigilance?

For WHO and WHO Collaborating Centres

- To establish a platform for sharing experience and resources for measuring the impact of PV.
- To create a tool-kit for training in planning an intervention and impact evaluation.
- To investigate if the WHO indicators capture impact.

Working group six: Role of pharmacovigilance centres in promoting quality use of medicines

Moderators: Shirly Samson Varughese, Ministry of Health, Oman; and Victoria Nambasa, NDA, Uganda

Rapporteur: Rogers Sekabira, Pharmacy Services Coordinator, Uganda

Representatives from 20 Member States (Brazil, Burkina Faso, Cambodia, Democratic Republic of Congo, Ethiopia, Kenya, Lao Peoples Democratic Republic, Kyrgyzstan, Mali, Mauritius, Morocco, Namibia, Oman, Pakistan, Sierra Leone, Thailand, Uganda, Vietnam, Zambia and Zimbabwe) participated in the working group discussions. The group discussed how PV could be translated into knowledge and practice, and shared how PV data informs clinical practice. Examples of how PV translates to clinical practice include: averting medication errors associated with dosing changing treatment guidelines of antiretroviral therapy (ART) following identification of lipodystrophies associated with stavudine (D4T); improvement of patient safety and care by informing health care professionals of a signal for an ADR with vancomycin. The group recognized the value of drug utilization studies and their potential to improve clinical practice by identifying irrational use of medicines. Challenges identified included: poor use of data by medicines and therapeutic committees to guide therapeutic decisions and clinical practice. The group advocated a holistic approach in the provision of care.



Recommendations for working group six: Role of pharmacovigilance centres in promoting quality use of medicines

For National Pharmacovigilance Centres

- To collaborate with all stakeholders (regulators, universities, organizations, consumers).
- To promote quality use of medicines

- To evaluate links between pharmacovigilance centres with medicines and therapeutic committees (rational drug unit) for the rational use of medicines within countries, build collaborations and clearly define roles.
- To encourage governments to implement PV and use this data to promote quality use of medicines.
- To have a strategy to communicate and harmonize messages on rational use of medicines in public and private sectors.

For WHO and WHO Collaborating Centres

- To develop guidelines offering holistic management of ADRs and support their implementation

To continue to address the issue of substandard and falsified medicines.

Working group seven: Communications of pharmacovigilance actions

Moderators: Heather Morrison, Health Canada, Canada; and Martina Schäublin, Swissmedic Switzerland

Rapporteur: Mick Foy, Medicines and Healthcare products Regulatory Agency (MHRA)

Representatives from 11 Member States (Barbados, Brazil, Burkina Faso, Canada, Egypt, Haiti, Morocco, Singapore, Switzerland, Uganda, UK) shared examples on how they share PV actions with the public. Communication channels depend on the target audience. Various electronic methods are used: e-mail, point of care alerts via electronic prescribing system, website, and increasingly social media (Facebook). Paper-based media are posters/flyers, printed bulletins, Dear HCP letters, comics for children. Concerns about direct communications without the involvement of PV centres to the public were raised, for example drug scares compromising public health programmes and affecting compliance.



Recommendations for working group seven: Communications of pharmacovigilance actions

For WHO and WHO Collaborating Centres

- Develop standardised training, including media training, on developing PV messages..
- Develop methods on how to measure success of communication.
- Support with relevant resources (technologies) and compile stories of successful communication campaigns from Member States.
- Create standard messages on topics such as online purchases and unlicensed medicines

For all

- Provide general public health awareness messages on topics such as online purchases and unlicensed medicines
- Include key pharmacovigilance messages in campaigns to encourage reporting.

Working group eight: Benefit-harm assessment approaches

Moderators: Shanthi Pal, WHO Headquarters, Switzerland; and Christopher Keung, Swiss medic, Switzerland

Rapporteur: Rohini Fernandopulle, General Sir John Kotelawala Defence University, Sri Lanka, and Ibrahim Ali, Otulukp, NAFDAC, Nigeria.

The working group reviewed case studies and listed various factors that should be considered in benefit-harm assessments associated with medicinal products. Assessment of benefit-risk is conducted at a global, regional, national, subgroup, and patient level. Data sources for assessment included the literature, summary of product characteristics (SPCs), PSURs, public assessment reports (PARs), clinical trials, electronic patient records, patient feedback, expert opinion, patient outcome databases, and national pharmacovigilance centres. The group compared the use of pre and post registration data. The group discussed the need for benefit-harm assessments to be multidisciplinary, tools for quantitative assessments and policies.



Recommendations for working group eight: Benefit-harm assessment approaches

For WHO and WHO Collaborating Centres

- To develop technical guidance tools.
- To support member states in benefit-harm assessments.
- To share assessment reports.
- To facilitate training and mentoring activities on benefit harm assessments.
- To discuss the development of benefit harm assessments tools with Council for International Organizations of Medical Sciences (CIOMS).

For National Pharmacovigilance Centres

- To promote the concepts of benefit-harm assessments in clinical meetings and undergraduate curricula.
- Mature centres to provide methods and training on benefit-harm assessment to less mature centres.
- To encourage the introduction of benefit-harm assessments as a component of an undergraduate pharmacovigilance curriculum.