

**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 titled PV strengthening in Armenia and Kyrgyzstan using smart safety surveillance approach; identifying gaps.

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Antihistamines (first generation, oral sedating)

Potential for fatal respiratory depression in children under two years of age

Australia. The Therapeutic Goods Administration (TGA) will work with manufacturers to strengthen warnings in the product information (PI) and consumer medicine information (CMI) for first generation oral antihistamines, to emphasize that they should not be used in children under two years of age due to the potential risk respiratory depression. In addition, TGA will be seeking to include a mandatory warning statement on labels of over-the-counter (OTC) liquid oral formulations of first-generation oral sedating antihistamines about the contra-indication of use in children under two years.

The TGA recently reviewed a fatal case of respiratory depression in a 74-day old infant who was treated with OTC promethazine oral liquid. Although the infant's death was not attributed to use of promethazine, the case raised a safety concern.

Up until 15 November 2017, the TGA database of adverse event notifications contained 45 reports of adverse events in children aged under two years in which a first-generation oral sedating anti-histamine is listed as the sole-suspected medicine. These reports document a range of adverse events including hypersensitivity reactions, agitation, abnormal movements, vomiting and diarrhoea.

Reference: Medicines Safety Update, TGA, Vol. 9, No. 1, February-March 2018 (www.tga.gov.au)

Clarithromycin

Potential risk of heart problems or death in patients with heart disease

USA. The US Food and Drug Administration (FDA) has added a new warning about an increased risk of death in patients with heart disease to the drug labels for clarithromycin (Baxin®). In addition, the FDA has added the results of a clinical trial that indicate this increased risk to clarithromycin drug labels.

Clarithromycin is used to treat a variety of infections and is not approved to treat heart disease.

The FDA's recommendation is based on a review of the results of a 10-year follow-up study of patients with coronary heart disease form a large clinical trial that first observed this safety issue. Results from the trial provide evidence of the increased risk compared to placebo. Other observational studies showed mixed findings. The FDA is unable to determine why the risk of death is greater for patients with heart disease.

Reference: Safety Alerts for Human Medical Products, US FDA, 2 February 2018 (www.fda.gov)

Clopidogrel and selexipag interaction

Co-administration is contraindicated due to increased blood concentrations of selexipag

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for clopidogrel containing products (Plavix®, ComPlavin®) and selexipag (Uptravi®) should be revised to include that co-administration of selexipag and clopidogrel is contraindicated.

Selexipag is indicated for pulmonary arterial hypertension. Clopidogrel is indicated for suppression of recurrent ischemic cerebrovascular disorder.

Clopidogrel is a potent CYP2C8 inhibitor and there is a possibility of an onset of adverse drug reactions and/or symptom exacerbation arising from an increase in blood concentrations of selexipag and its active metabolite. MHLW and PMDA have conducted an investigation and have concluded that the revision of the package inserts of both products should include language regarding the risks associated with co-administration of clopidogrel.

Reference: Revision of Precautions, MHLW/PMDA, 20 March 2018 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletters No.5, 2017: Contraindication with potent inhibitors of cytochrome P450 2C8 in Spain)

Daclizumab beta

Immediate suspension: risk of serious inflammatory brain disorders

Europe. The European Medicines Agency (EMA) has recommended the immediate suspension and recall of daclizumab beta (Zinbryta®) following 12 reports of serious inflammatory brain disorders worldwide, including encephalitis and meningoencephalitis in patients with multiple sclerosis. Three of the cases were fatal.

Daclizumab beta is indicated for treating relapsing forms of multiple sclerosis. Following a 2017 review of the medicine's effects on the liver, the use of the medicine was restricted to patients who have tried at least two other disease-modifying treatments and cannot be treated with other multiple sclerosis treatments.

Also, the available evidence indicate that immune reactions

observed in the reported cases may be linked to the use of daclizumab beta.

To protect patients' health, EMA is recommending the immediate suspension of the medicine's marketing authorisation in the EU and a recall of batches from pharmacies and hospitals.

EMA advises that no new patient should start treatment with daclizumab beta. Health-care professionals should immediately contact patients currently being treated with daclizumab beta, stop treatment, and consider alternatives. Patients stopping treatment must be followed up for at least six months.

EMA's recommendation to suspend daclizumab beta and recall the product is being sent to the European Commission for a legally binding decision.

The company that markets daclizumab beta has already voluntarily requested a withdrawal of the medicine's marketing authorisation and informed EMA of its intention to stop clinical studies.

Reference:

EMA, 2 and 7 March 2018 (www.ema.europa.eu)

Dipeptidylpeptidase-4 inhibitors

1. Potential risk of a skin reaction (bullous pemphigoid)

Canada. Health Canada has requested that the product information for dipeptidylpeptidase-4 (DPP-4) inhibitors (alogliptin, saxagliptin, sitagliptin, and linagliptin) is updated to include the risk of bullous pemphigoid.

DPP-4 inhibitors, known as gliptins are prescription medicines indicated for type-2 diabetes in adults.

A total of 24 serious international reports of

potential bullous pemphigoid with the use of alogliptin (16) and saxagliptin (8) were identified by manufacturers and from a search in the Canada vigilance database. All 24 reports were considered to show a possible link between the skin reaction and the drug. Of the 24 reports, three deaths were reported, one of which was considered to be possibly linked to bullous pemphigoid from using the DPP-4 inhibitor.

Health Canada's review concluded that there may be a link between any of the DPP-4 inhibitors and the risk of bullous pemphigoid. Health Canada will publish a notice in the Health Product InfoWatch to inform Canadians and health-care professionals of this new safety information.

Health Canada will continue to monitor safety information involving DPP-4 inhibitors to identify and assess potential harms.

Reference:

Summary Safety Review, Health Canada, 25 January 2018 (www.hc-sc.gc.ca)

2. Risk of acute pancreatitis (anagliptin, linagliptin, teneligliptin)

Japan. MHLW and PMDA have announced that the package inserts for anagliptin (Suiny®), linagliptin (Trazenta®), and teneligliptin containing products (Tenelia®, Canalia Combination®) should include acute pancreatitis and pemphigoid (anagliptin) as clinically significant adverse reactions.

Dipeptidyl peptidase-4 (DPP-4) inhibitors and are indicated to treat hyperglycemia in adults with two diabetes mellitus.

Cases of acute pancreatitis have been reported in patients treated with anagliptin (four cases), linagliptin (19 cases), and teneligliptin hydrobromide hydrate (9 cases) in Japan. In addition, seven cases of pemphigoid were reported in

patients treated with anagliptin. MHLW and PMDA have concluded that revision of the package insert was necessary following the investigation of available evidence and consultations with expert advisors.

Reference:

Revision of Precautions, MHLW/PMDA, 20 March 2018 (www.pmda.go.jp/english/)

Efavirenz

Risk of prolonged QT

Japan. MHLW and PMDA have concluded that revision of the package insert for efavirenz (Stocrin Tablets®) should be revised to include the risk of prolonged QT as a precaution.

Efavirenz is indicated for HIV-1 infection. Prolonged QT interval was observed in conjunction with increased blood concentrations of efavirenz in an overseas clinical study investigating the effect of this drug on the QT interval. Several cases of prolonged QT have also been reported in patients treated with efavirenz overseas. No cases involving prolonged QT have been reported in the last three fiscal years in Japan.

Reference:

Revision of Precautions, MHLW/PMDA, 13 February 2018 (www.pmda.go.jp/english/)

Flupirtine

Withdrawal due to serious liver problems

Europe. The EMA has recommended that the market authorization for flupirtine should be withdrawn due to the risk of serious liver injury. The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) has endorsed the EMA's decision.

Flupirtine is used to treat acute pain (up to 2 weeks) in

patients who cannot use other painkillers such as opioids or nonsteroidal anti-inflammatory medicines (NSAIDs).

The EMA's recommendation was an outcome following a review of flupirtine carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), who looked at the available data including studies evaluating whether risk minimization measures set in 2013 were followed in clinical practice.

Since 2013, there were reports of serious liver injury with flupirtine use. These included 23 cases of acute liver failure, some of which were fatal or led to transplantation.

PRAC concluded that the restrictions introduced in 2013 have not been sufficiently followed, and cases of serious liver injury, including liver failure, still occurred.

The CMDh therefore agreed that patients taking flupirtine-containing medicines continue to be exposed to serious risks which outweigh the benefits of these medicines. Alternative treatment options to flupirtine are available.

Reference: EMA, 23 March 2018 (www.ema.europa.eu)
(See WHO Pharmaceuticals Newsletters No.3, 2013: Review started due to concerns over liver problems in Europe)

Gadolinium-containing contrast agents

Omniscan® and intravenous iv Magnevist® no longer authorised; and restrictions of use for other linear agents

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that two gadolinium-containing contrast agents (Omniscan® and intravenous Magnevist®) are now no longer authorized

for use and a product recall of any existing unexpired stock is underway, due to risk of gadolinium deposition in the brain with use of linear gadolinium-containing contrast agents. In addition, the linear agents gadobenic acid and gadoxetic acid (Primovist®) will be limited for use in liver imaging and when imaging in the delayed phase liver is required.

Gadolinium-containing contrast agents (GdCAs) are indicated for the enhancement of magnetic resonance imaging (MRI). GdCAs can be divided into two groups: linear and macrocyclic. The use of linear GdCAs has decreased markedly in the UK, following advice published in 2006 which aimed to reduce risk of nephrogenic systemic fibrosis (NSF).

In view of evidence of retention of gadolinium in brain and other tissues, the risks of gadodiamide and intravenous gadopentetic acid are considered to outweigh their benefits.

There are other GdCAs that will remain on the market, but should only be used when diagnostic information is essential and not available with unenhanced MRI.

Reference:
Drug Safety Update, MHRA, 6 February 2018 (www.gov.uk/mhra)
(See WHO Pharmaceuticals Newsletters No.1, 2018; No.4 and 5, 2017; No.5, 2015; No.6, 2013: for related information)

Hydroxyethyl-starch solution

Risk of kidney injury and death in certain patient populations

Europe. The EMA has recommended the withdrawal of the market authorization license for hydroxyethyl-starch (HES) solutions for infusion due to risk of kidney injury. This has been endorsed by CMDh.

HES solutions for infusion are used for the management of hypovolaemia caused by acute blood loss, where treatment with alternative infusion solutions known as crystalloids alone is not considered to be sufficient.

A review of the safety of HES solutions for infusion has been carried out by EMA's PRAC. HES solutions have continued to be used in critically ill patients and patients with sepsis despite the introduction of restrictions on use in these patients in 2013. The final decision to withdraw the market authorization license, however, will be taken by the European Commission.

Reference:
EMA, 26 January 2018 (www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletters No.6, 2017: New review of benefit-risk balance in Europe; No.4, 2017: Acute kidney injury in non-critically ill patients: not enough evidence in Canada; No.1, 2015: Contraindications and warnings in the United Kingdom and Canada)

Iohexol, Iomeprol

Risk of acute generalized exanthematous pustulosis

Japan. MHLW and PMDA have requested the revision of the package inserts for iohexol (Omnipaque®) and iomeprol (Iomeron®) to include the risk of acute generalized exanthematous pustulosis as a clinically significant adverse reaction.

Iohexol and imeprol are indicated for various angiography and x-ray procedures.

Two cases of acute generalized exanthematous pustulosis were reported in patients who used iomeprol and iohexol in the last three fiscal years in Japan. A causal relationship with the products could not be excluded for those patients. No fatal cases have been reported.

Reference:
Revision of Precautions,

MHLW/PMDA, 13 February 2018 (www.pmda.go.jp/english/)

Kampo medicines containing Gardenia fruit

Risk of mesenteric phleboscrosis

Japan. MHLW and PMDA have recommended that the package insert for Japanese traditional medicines containing Gardenia fruit should be revised to include the risk of mesenteric phleboscrosis as a precaution.

Gardenia fruit preparations have various indications, for example coughing, constipation, obesity and others.

A total of 86 cases of mesenteric phleboscrosis were reported in the last three fiscal years in Japan. A causal relationship was evaluated in the 20 cases out of 86 cases. A causal relationship could not be excluded in 14 cases. No fatal cases were reported.

Reference:

Revision of Precautions, MHLW/PMDA, 13 February 2018 (www.pmda.go.jp/english/)

Miconazole and warfarin interaction

Reminder of reduced warfarin clearance

Australia. TGA has requested that a warning statement about the potential interaction with warfarin is added to product labels for miconazole containing products. In addition, TGA will also work with manufacturers to strengthen warnings in the patient information (PI) and consumer medicines information (CMI) documents.

Miconazole is an antifungal medication used to treat ringworm, pityriasis versicolor,

and yeast infections of the skin or vagina.

Miconazole inhibits one of the main cytochrome P450 isoenzymes involved in warfarin metabolism (CYP2C9), which can result in reduced warfarin clearance and an enhanced anticoagulant effect.

This can lead to supra-therapeutic international normalised ratio (INR) values and subsequent bleeding complications. Bleeding events can have fatal outcomes.

The TGA has reminded health professionals that, while the number of Australian reports of warfarin and miconazole interactions are low, the potential of an interaction can be life-threatening.

Reference:

Medicines Safety Update, TGA, Vol. 9, No. 1, February-March 2018 (www.tga.gov.au)

(See WHO Pharmaceuticals Newsletters No.6, 2016: Risk of bleeding due to drug-drug interaction in Japan; No.4, 2016: Potential for serious drug-drug interactions with warfarin in the United Kingdom)

Mycophenolate mofetil, mycophenolic acid

Contraception is recommended

Ireland. Mycophenolate (mycophenolate mofetil and mycophenolic acid) is authorized to prevent transplant rejection, and is a major human teratogen known to cause miscarriages and congenital malformation in pregnant women. Also, mycophenolate medicines are genotoxic.

The Health Products Regulatory Authority (HPRA) has updated contraceptive advice for male patients. Male patients taking mycophenolate-containing medicines or their partners should use reliable contraception during treatment and for 90 days after finishing treatment.

Women of child bearing potential should use at least one form of reliable contraception before starting treatment, during treatment and for six weeks after stopping treatment. Two forms of contraception are preferred.

Reference:

Drug Safety Newsletter, HPRA, 16 March 2018 (www.hpra.ie)

United Kingdom. MHRA has updated contraception advice for male patients on mycophenolate mofetil.

The available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate medicines, but there is insufficient evidence to exclude any risk.

As a precautionary measure for male patients, it is now recommended that either the patient or their female partner use reliable contraception during treatment with mycophenolate medicines and for at least 90 days after stopping. Female patients of childbearing potential receiving mycophenolate should always use contraception.

Reference:

Drug Safety Update, MHRA, 6 February 2018 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletters No.2, 2016: Contraindications relating to pregnancy and breastfeeding in Australia; No.1, 2016: New pregnancy-prevention advice for women and men in the United Kingdom)

Radium-223 dichloride

Not to be used together with abiraterone and prednisone/prednisolone

Europe. EMA recommends that radium-223 dichloride (Xofigo®) should not be used in combination with abiraterone acetate (Zytiga®) and prednisone/prednisolone, due

to an increased risk of death and fractures.

Radium-223 is used to treat prostate cancer in adult men. It is authorised for use when medical or surgical castration does not work, and when the cancer has spread to the bones and is causing symptoms such as pain but is not known to have spread to other internal organs.

EMA's PRAC has reviewed preliminary data from an ongoing clinical study in metastatic prostate cancer patients. In this study 34.7% of patients treated with radium-223, abiraterone and prednisone/prednisolone have died, compared with 28.2% of patients given placebo, abiraterone and prednisone/prednisolone.

The restriction in use is a temporary measure until the ongoing in-depth review of the benefits and risks of radium-223 is complete. The EMA will communicate further once the review has been concluded.

Reference: EMA, 9 March 2018 (www.ema.europa.eu)

Retinoids

Updated measures for pregnancy prevention and potential risk of neuropsychiatric disorders

Europe. EMA's PRAC has completed a review of retinoid medicines and has recommended that pregnancy prevention measures need to be updated. In addition, prescribing information for oral retinoids should be updated to include a warning on the possibility of neuropsychiatric disorders.

Oral retinoids are used to treat various forms of severe acne, severe hand eczema that does not respond to treatment with corticosteroids, severe forms of psoriasis and other skin conditions, and certain types of cancer. Retinoids applied to the

skin are used to treat various skin conditions including mild to moderate acne.

The review confirmed that oral retinoids can harm the unborn child and must not be used during pregnancy.

Data on neuropsychiatric adverse events was not sufficient to assess the risk with retinoid use. However, considering that patients with severe skin conditions may be more vulnerable to neuropsychiatric disorders due to the nature of the disease, the prescribing information for oral retinoids will be updated to include a warning about this possible risk.

Reference: EMA, 23 March 2018 (www.ema.europa.eu)
(See WHO Pharmaceuticals Newsletters No.1, 2015: Possible risk of psychiatric disorders in the United Kingdom)

Sterile talc

Risk of shock and anaphylaxis

Japan. MHLW and PMDA have announced that the package insert for sterile talc (Unitalc Intrapleural Suspensions®) should be revised to include shock and anaphylaxis as clinically significant adverse reactions.

Sterile talc is indicated for prevention of recurrent malignant pleural effusion.

A total of three cases associated with shock and/or anaphylaxis were reported in patients treated with sterile talc in Japan. Based on the results of an investigation of available evidence and in consultation with expert advisors, MHLW and PMDA have concluded that revision of the package insert was necessary.

Reference: Revision of Precautions, MHLW/PMDA, 20 March 2018 (www.pmda.go.jp/english/)

Tolvaptan

Risk of acute hepatic failure

Japan. MHLW and PMDA have announced that the package insert for tolvaptan (Samsca®) should be revised to include risk of hepatic failure.

Tolvaptan is indicated for treatment of fluid retention in heart failure and hepatic cirrhosis when treatment with other diuretics is not sufficiently effective; and to slow the progression of autosomal dominant polycystic kidney disease.

Cases of acute hepatic failure have been reported in patients treated with tolvaptan in Japan. A total of 11 cases associated with acute hepatic failure have been reported to date (including four cases for which a causal relationship with the product could not be ruled out). Seven of these 11 cases were fatal (including three cases for which a causal relationship with the product could not be ruled out).

Reference: Revision of Precautions, MHLW/PMDA, 20 March 2018 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletters No.3, 2013: Limits duration and usage due to possible liver injury leading to organ transplant or death in the United States; No.2, 2013: New warning regarding a potential risk of liver damage in Canada; No1, 2013: Potential risk of liver injury in the United States)

Artemisia annua extract in grape seed oil

Potential risk of harm to the liver

New Zealand. The Medicines and Medical Devices Safety Authority (Medsafe) has advised health-care professionals to consider liver toxicity as a possible adverse effect of *Artemisia annua* (Arthrem®).

Artemisia annua is a natural dietary supplement used for maintaining and supporting joint health and mobility.

The Centre for Adverse Reactions Monitoring (CARM) received 14 reports of liver toxicity associated with the use of *artemisia annua*. Many of the reports included jaundice as a reaction. All of the patients stopped taking *artemisia annua*, and at the time of reporting most had already recovered or were improving.

Medsafe advises health-care professionals to advise patients/consumers experiencing liver problems and taking *artemisia annua* or other natural health products, to stop taking the product and contact their general practitioners.

Reference:

Safety Information, Medsafe, 15 February 2018 (www.medsafe.govt.nz/)

Aspirin in chloroform

Potential risk of harm to the liver

New Zealand. Medsafe has announced that CARM received a report of a death of a female, who developed hepatotoxicity suspected by the treating physicians to be linked to topical application of aspirin in chloroform.

Aspirin in chloroform is compounded by pharmacists

and pharmacy technicians and is used in the treatment of post herpetic neuralgia. A study conducted in 1993 found that chloroform did not improve the efficacy of the topical aspirin preparation, but improved its solubility. There is no convincing evidence in the scientific literature to indicate that aspirin dissolved in chloroform is effective for post-herpetic neuralgia.

Chloroform is classified by the International Agency for Research on Cancer (IARC) as a group 2B carcinogen, being possibly carcinogenic to humans. Significant exposure to chloroform has been associated with hepatotoxicity in humans. This is a potential risk for patients who are applying aspirin in chloroform multiple times per day for extended periods of time.

Given the lack of evidence for efficacy and significant risk of harm, the benefit-risk balance for topical aspirin in chloroform is unfavourable and prescribers should use alternative medicines for their patients.

Reference:

Safety Information, Medsafe, 1 March 2018 (www.medsafe.govt.nz/)

Clozapine

Risk of agranulocytosis

Canada. Health Canada has requested that manufacturers of clozapine (Clozaril®) submit a report, in two years, of all data collected in relation to agranulocytosis with use of clozapine.

Clozapine is indicated to treat symptoms of schizophrenia in adults when other drugs have not helped. Agranulocytosis is a known adverse drug reaction that can occur in association with clozapine use. For this reason, white blood cell levels are monitored periodically in patients treated with clozapine to make sure that they do not become too low.

During routine safety review activities, concerns were raised about whether or not processes to monitor agranulocytosis were effective. Health Canada reviewed all of the available evidence related to the effectiveness of the white blood cell monitoring measures currently in place for clozapine.

From 1991 to the time of the review, Health Canada has received 92 Canadian reports of low numbers of white blood cells in patients using clozapine. A review of these reports found that 11 of them were possibly linked to clozapine use.

The review concluded that monitoring measures that are in place to detect low numbers of white blood cells are acceptable, however this risk should still be monitored. Therefore, Health Canada has asked that the manufacturers of clozapine submit a report, in two years, of all the data related to the risk of agranulocytosis with clozapine use.

Reference:

Summary Safety Review, Health Canada, 9 March 2018 (www.hc-sc.gc.ca)
(See WHO Pharmaceuticals Newsletters No.5, 2015: Modifications for monitoring neutropenia in the United)

Dabigatran

Possible risk of gout or gout-like symptoms

New Zealand. Medsafe highlighted a possible risk of gout or gout-like symptoms with the use of dabigatran (Pradaxa®).

Dabigatran is used in conditions such as: prevention of stroke and systemic embolism; prevention of venous thromboembolism; treatment and prevention of deep vein thrombosis and/or pulmonary embolism.

In September 2017 a report of aggravation of gout after starting treatment with

dabigatran was received by the CARM. The patient experienced a marked increase in episodes of gout after starting dabigatran and improved after treatment with dabigatran was stopped, without other interventions.

Gout is not a known adverse effect of dabigatran and is not included in the data sheet. A search of the WHO global database for Individual Case Safety Reports, VigiBase to date, revealed 71 reports worldwide of gout or gout-like symptoms, suspected to be associated with dabigatran use.

Medsafe is placing this safety concern on the medicines monitoring scheme to obtain further information on these possible adverse reactions.

Also, Medsafe calls for reports of cases of gout or gout-like symptoms in patients taking dabigatran.

Reference:

Safety Information, Medsafe, 31 January 2018
(www.medsafe.govt.nz/)

Direct-acting antivirals (DAAs)

Possible effects on blood glucose control when used in patients with type 2 diabetes

New Zealand. Medsafe investigated the association of direct-acting antivirals (DAAs) and effects on blood glucose control when used in patients with type 2 diabetes. During the medicines monitoring period (13 March 2017 to 31 December 2017), no cases of abnormal glucose levels were reported to the CARM.

Effects of the use of DAAs on blood glucose control, when used in patients with type 2 diabetes, could not be confirmed.

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

Medsafe will re-investigate this concern should more information become available.

Reference:

Safety Information, Medsafe, 31 January 2018
(www.medsafe.govt.nz/)

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

Eribulin

Potential risk of severe skin adverse effects

Canada. Health Canada reviewed the risk of rare, severe skin adverse effects (Severe Cutaneous Adverse Reactions, SCAR) with the use of eribulin (Halaven®), following a Canadian report of erythema multiforme which was a potential case of SCAR.

Eribulin is a prescription drug that is indicated to treat various types of breast and soft tissue cancers (liposarcomas).

There is no Canadian report of SCAR. This safety review looked at 22 international cases of SCAR with the use of eribulin from the manufacturer's global safety database. Of these 22 cases, five cases were found to be possibly linked to the use of Eribulin.

Both Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) have already been included in the product safety information by Health Canada, the European Medicines Agency (EMA), and US FDA.

Health Canada's review concluded that there was not enough evidence to establish a direct link between the use of eribulin and the potential risk of SCAR. The current product safety information covers the potential risk of SCAR and not additional warnings are required.

Reference:

Summary Safety Review,

Health Canada, 12 March 2018
(www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletters No.2, 2016 Risks of oculomucocutaneous syndrome (Stevens-Johnson Syndrome) and erythema multiforme in Japan)

Idarucizumab

A second dose may be needed

New Zealand. Prescribers are alerted to the possibility that some patients may need a second dose of idarucizumab (Praxbind®) to reverse the effects of dabigatran (Pradaxa®) for patients requiring emergency procedures with a risk of uncontrolled bleeding.

Idarucizumab is used for rapid reversal of dabigatran's anticoagulant effect for emergency surgery/urgent procedures, or in life-threatening or uncontrolled bleeding.

The recommended dose of idarucizumab is 5 g administered intravenously. Post-marketing experience with dabigatran has shown that a second dose of idarucizumab is sometimes required.

Administration of a second 5 g dose of idarucizumab may be considered in patients with prolonged clotting times who develop a recurrence of bleeding or who require a second emergency surgery/urgent procedure. Medsafe advises referring to the data sheet for further information.

Reference:

Safety Information, Medsafe, 1 March 2018
(www.medsafe.govt.nz/)

Ruxolitinib

Potential risk of liver injury

Canada. Health Canada reviewed safety information on the risk of liver injury with ruxolitinib (Jakavi®) use.

Ruxolitinib is used to treat certain types of blood cancers.

The review was carried out following an international report of a suspected serious liver injury from an ongoing study that used ruxolitinib to treat patients.

Although the risk of liver injury is not mentioned in the safety information for ruxolitinib, it is recommended that health-care professionals test the patient's blood before and during treatment for signs of liver problems.

Health Canada reviewed one Canadian report of liver injury and 25 international patient reports of liver injury or liver failure with the use of ruxolitinib. A possible link between liver problems and the use of ruxolitinib was found in 11 reports, but it was not possible to determine whether ruxolitinib itself caused the liver problems as patients either took other medicines or had co-existing diseases that could cause liver injury.

Health Canada's review concluded that the evidence does not show a link between ruxolitinib and the risk of liver injury. The safety information for the drug is appropriate at this time. Health Canada will continue to monitor the safety of ruxolitinib.

Reference:

Summary Safety Review, Health Canada, 26 February 2018 (www.hc-sc.gc.ca)

Sodium-glucose Cotransporter-2 (SGLT2) inhibitors

Potential risk of a rare brain condition (posterior reversible encephalopathy syndrome) in patients who developed diabetic ketoacidosis

Canada. Health Canada has reviewed the potential risk of posterior reversible

encephalopathy syndrome (PRES) in patients were treated with sodium-glucose co-transporter 2 (SGLT2) inhibitors and developed diabetic ketoacidosis.

SGLT2 inhibitors lower blood sugar in adults with type 2 diabetes.

At the time of the review, Health Canada had received two unique Canadian reports of PRES in patients treated with SGLT2 inhibitors who had developed DKA. Both reports involved canagliflozin and suggested that PRES could possibly be associated with the medicine. However, other risk factors such as DKA and severe infection could have played a role in the events.

Health Canada's review of the available information did not find a link between the use of SGLT2 inhibitors and the risk of PRES in patients who have developed DKA.

Health Canada encourages consumers and healthcare professionals to report any adverse effects related to the use of these health products. Health Canada will continue to monitor the safety of SGLT2 inhibitors.

Reference:

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

Suvorexant

Next day residual effects

Australia. TGA has advised health professionals to discuss potential adverse events, especially next day residual effects (drowsiness), with patients before prescribing suvorexant (Belsomra®).

Suvorexant is indicated for the treatment of insomnia, characterised by difficulties with sleep onset and/or sleep maintenance.

Since registration, the TGA has received a number of reports of adverse events, including sleep

paralysis, gait disturbance, hallucination, headache and paraesthesia.

Reference:

Medicines Safety Update, TGA, Vol. 9, No. 1, February-March 2018 (www.tga.gov.au)

Ulipristal acetate

Potential risk of liver injury

Europe. EMA's PRAC is currently reviewing the benefits and risks with ulipristal acetate (Esmya®), following reports of serious liver injury, including liver failure leading to transplantation.

Ulipristal was authorized in the EU in 2012 for the treatment of moderate to severe symptoms of uterine fibroids.

As a temporary measure while the review is ongoing, the PRAC has recommended regular liver monitoring for women taking ulipristal for uterine fibroids.

All women taking ulipristal should have a liver function test at least once a month during treatment. If the test is abnormal (liver enzyme levels more than two times the upper limit of normal), the health-care professional should stop treatment and closely monitor the patient. Liver tests should be repeated two to four weeks after stopping treatment.

The PRAC is also recommending that no new patients should be started on ulipristal and no patients who have completed a course of treatment should start another one for the time being. A link between ulipristal and cases of serious liver injury is under review.

An EU-wide review of ulipristal started in December 2017 following reports of serious liver injury in women using the medicine. The review is ongoing; however, temporary safety measures were considered necessary following receipt of the fifth case of

hepatic failure (the fourth that required liver transplantation).

Reference:

EMA, 9 February 2018
(www.ema.europa.eu)

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. 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.

Artemether/Lumefantrine and Stevens-Johnson syndrome: a recommendation for continued vigilance in malaria-endemic areas

Dr. Birgitta Grundmark, Uppsala Monitoring Centre and Pramod Kumar Adusumilli, the National Coordination Centre for Pharmacovigilance Programme of India

Summary

A signal was detected on the serious cutaneous adverse drug reaction (ADR) Stevens-Johnson syndrome (SJS) in relation to the anti-malarial fixed drug combination Artemether/Lumefantrine (ALU) during a signal detection screening focused on reporting patterns in Africa, Asia and Latin America. In the WHO global database of individual case safety reports, VigiBase, as of March 2017 there were 19 reports on this drug-ADR combination. Most reported cases contain relatively little information, the time to onset is somewhat atypical and alternative explanations may have contributed. As other cutaneous reaction terms describing conditions with a clinical closeness to SJS are included in labelling for ALU in parts of the world, this, along with the seriousness of the reaction, is the reason to signal the combination to raise awareness of this issue.

Introduction

Fixed-dose combinations of Artemether/Lumefantrine (ALU) are available globally and recommended as one of the first line treatments of uncomplicated malaria (Pl. Falciparum) in infants, children and adults.¹ The combination is neither indicated for severe malaria nor for prevention of malaria. A typical treatment course would be six doses consisting of 1-4 tablets per dose over three days.²

Stevens-Johnson syndrome (SJS) is a severe mucocutaneous immune reaction, characterized by necrosis and detachment of the epidermis of the skin through apoptosis of keratinocytes.³ Common prodromal symptoms of SJS are flu-like symptoms such as fever, sore throat, headache and fatigue, which may initially be misdiagnosed as an infection and treated as such. Typically, a maculopapular blistering skin rash abruptly arises on the face, torso and may spread to arms, legs and soles. Oral, ocular or genital mucous membranes are affected in a majority of patients.

The most common cause of SJS is drugs, including anti-malarials. The condition may also be triggered by malignant disease and infections, and regarding the latter, protozoal infections such as malaria and trichomoniasis have been described as causal factors.⁴ In a significant proportion of the cases no clear causal factor can be identified. Genetic factors such as being a slow acetylator may predispose to SJS. Stevens-Johnson syndrome and the closely related syndrome of toxic epidermal necrolysis (TEN) are variants of a disease continuum where in SJS skin detachment is <10% of the body surface area; in SJS/TEN overlap the area is 10-30% and in TEN involves detachment of >30% of the body surface.^{5,6} Onset is described as 1-30 days after start of instigating factor.

Literature and Labelling

United Kingdom, Australian and Swiss labels (Riamet®) are very similar and include as acknowledged adverse reactions of the drug combination: rash, urticaria and hypersensitivity, the latter without any further specification.² Angioedema and face edema are mentioned as reported from post marketing experience. An example of an Indian package insert (Lumerax®) includes rash, pruritus, urticaria, and angioedema.⁷ The United States Food and Drug Administration (US FDA) label (Coartem®) mentions the following regarding the post marketing experience: "hypersensitivity reactions: like [...] serious skin reactions (bullous eruption) have been reported". This could evidently encompass SJS while SJS is not included per se in the labelling.⁸

In an article describing an ADR reporting survey performed in Uganda one case is described as reported from a doctor where a "52 year old female on Coartem oral route developed sores on the whole body". No further information is available on the case which can be suspected of describing SJS or TEN.⁹

Reports in VigiBase

In VigiBase, the WHO global database of individual case safety reports, as of March 2017 there were 19 cases of the combination ALU and SJS among 832 reports in total for ALU. The reports originate from Tanzania (7), Ghana (5), India (3), Kenya (2), Democratic Republic of Congo (1) and Zambia (1), and were entered into the database from 2008 onwards.

In the 19 cases the median age of patients was 29 years, ranging from 2 to 64 years. Eleven of the cases concern males, five females, two reports contain ambiguous gender information and in one report the gender information is missing. Reporters were one patient and 18 health care professionals (HCPs), e.g. physicians, pharmacists and other HCPs.

All cases were reported as fulfilling serious criteria, with five explicitly stating the condition to be life-threatening and with one having a fatal outcome. At the time of reporting and apart from the patient who died, 13 of the patients had recovered or were recovering, two had not yet recovered and for three the outcome was unknown or not reported.

Clinical case histories

In most reports the case descriptions are very brief with only limited clinical data. Some merely state the diagnosis SJS while others describe in more detail skin blistering with desquamation and mouth,

eye or genital ulcerations. A few cases note a general spreading of the syndrome giving a suspicion they would fulfil the clinical definition of SJS/TEN or TEN. In many reports the full course of ALU appears to have been given although onset of symptoms occurred very rapidly after treatment initiation. One report explicitly mentions a positive malaria test whereas most cases state that the patient was treated for malaria or just states 'fever' as the treatment indication without providing further information. None of the reports contain any relevant history of previous use of, or reactions to, this or other drugs.

ALU monotherapy cases

In seven cases where ALU was the only reported drug, the time to onset (TTO) was reported as the same day in two cases, 1 day in two cases, 3 and 5 days in two other cases and in one case with a fatal outcome where the TTO was unknown, the patient died 10 days after onset.

Non-Monotherapy cases

In all the 12 cases which mention more than one drug as co-suspect or concomitant, at least one of the co-reported drugs is known to have the ability to cause SJS, e.g. phenytoin, valproic acid, carbamazepine, ceftriaxone, benzthiazine/triamterene, albendazole, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), carbamazepine and paracetamol. The median TTO of SJS from start of ALU in these cases was 1.5 days (unknown in two cases).

In the eight cases with co-reported paracetamol the starting date and hence the TTO (when noted) was the same as for ALU whereas in three cases reporting other co-reported/suspect drugs TTO for these were 3-27 days and one noted as "long term use". In most paracetamol cases, there was no end date noted, hence it is unknown whether this drug was continued or not.

Discussion

At the time of data retrieval there were 19 reports of SJS in relation to ALU treatment in VigiBase. The US labelling mentions *serious skin reactions (bullous eruption)* in the post marketing experience.⁸

As prodromal symptoms of SJS are fever, headache, sore throat and fatigue, there are alternative explanations to the association between ALU and SJS. An early stage SJS caused by another factor could be mistaken for malaria and treated as such or the malarial disease could be causing the SJS. The short

TTO of 0-2 days in most of the reported cases is somewhat atypical and does weaken the suspicion of a causal association between the drug and the reaction while not excluding it. The insidious start of SJS further makes an exact onset of the condition difficult to establish. There is limited information in the described cases on their respective diagnostic certainty of malaria.

The presence of paracetamol, NSAIDs or ASA as concomitant treatment in malaria or SJS would be expected but obviously also obscures any causality assessment. Since case descriptions and information are sparse, other potential but unaccounted-for causes of the SJS appearing within a reasonable timeframe are not possible to rule out, e.g. other infections and other drugs or traditional remedies used.

Conclusion

The US labelling mentions serious bullous skin reactions which could potentially include cases of SJS. The VigiBase case series gives some suspicion of a causal association between ALU and SJS albeit some arguments against such an association are also present within it. While a firm conclusion on causality cannot be drawn at this point, national centres in malaria endemic areas should be aware of this potential issue, monitor and be prepared to take precautionary steps nationally if considered necessary.

Acknowledgement: Professor Ambrose Isah, Nigeria and Daniele Sartori, Uppsala Monitoring Centre for valuable input.

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Addendum regarding similar anti-malaria drugs:

In VigiBase there is one report on the combination Artemether-SJS from Kenya, one report on ALU-TEN from India and one report on Artemether-TEN from France. Regarding other artemisinin class drugs or combinations, VigiBase contained 10 reports of SJS and 4 of TEN. The observed number did not exceed the statistically expected for any of the combinations. 10 of the 14 reports were related to the use of artesunate and present a picture similar to the described for ALU, i.e. sparse information, predominately short times to onset and several co-suspect concomitant drugs. Neither rash nor more severe (systemic) skin reactions appear to be labelled for artesunate.

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Introduction

This document provides Novartis' comment on the draft of "Artemether/Lumefantrine and Stevens-Johnson syndrome: continued prospective pharmacovigilance suggested" which will be published in Signal from UMC – WHO Collaborating Centre for International Drug Monitoring.

The draft report concludes: "The US labelling mentions serious bullous skin reactions which could potentially include cases of SJS. The VigiBase case series gives suspicion of a causal association between ALU and SJS although some arguments against such an association are also present within it. While a firm conclusion on causality cannot be drawn at this point, national centres should be aware of this potential issue, monitor and be prepared to take precautionary steps nationally if considered necessary."

Background

Coartem/Riamet (artemether/lumefantrine) was first registered in 1998 and Novartis Pharma is currently the MAH in over 67 countries. The combined cumulative exposure for all formulations of Coartem/Riamet is estimated to be over 970 million patients (8 million PTY).

Serious skin reactions, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are being closely monitored in the Coartem/Riamet PSURs as potential risk. In the last PSUR (01 Nov 2013 – 01 Oct 2016) assessment Report, the Pharmacovigilance Risk Assessment Committee (PRAC) agreed with the company's assessment that no label change is warranted and monitoring of the topic should continue.

The Coartem USPI mentions under Postmarketing Experience serious skin reactions (bullous eruption), also stating that due to the voluntary reporting it is not always possible to establish a causal relationship to drug exposure.

It should be noted that, there are several generic formulations of artemether (synthetic and natural)-lumefantrine combinations on the market, including substandard or counterfeit medications.

Epidemiology

SJS and TEN are rare but life-threatening mucocutaneous diseases [Harr T et al., 2010]. Several drugs are associated with an increased risk of SJS/TEN including antiepileptics, antipsychotics, antimicrobials, antivirals, [Hirapara et al, 2017], allopurinol, analgesics like paracetamol [Khawaja et al 2012, Biswal et al, 2014], NSAIDs, COX-2 inhibitors, sertraline, [Roujeau et al., 1995; Mockenhaupt et al., 2008] and non-ACT antimalarials like sulfadoxine/pyrimethamine [Fansidar, PIL],

atovaquone and proguanil HCl [Malarone, SmPC] and mefloquine HCl [Lariam, SmPC]. SJS and TEN are also reported to occur at a higher incidence in HIV-infected persons [Knight et al, 2014].

Reported incidence rates of SJS/TEN range from 1.4 to 12.7 cases per million person-years [Diphhoorn et al., 2016; Rzany et al., 1996]. In a 1:4 matched case-control analysis Frey et al [Frey et al, 2017] found, that black and Asian patients were at a 2-fold risk of SJS/TEN when compared with white patients. This finding is particularly relevant because of the malaria endemic regions. Difficulties in obtaining definitive diagnoses of SJS and TEN are also a hurdle in estimating an accurate incidence [Yang et al 2016].

Methodology

Novartis global safety database was searched cumulatively through 30th Sep 2017 with SMQ narrow scope "Severe cutaneous adverse reactions" with Coartem/Riamet.

A literature review was also conducted based on searches in Medline, Embase and Biosis databases.

Results

Novartis safety database search

A total of eight cases were retrieved from the Novartis global safety database [Angola (3), Cameroon (1), France (1), Kenya (2) and Malawi (1)]. All cases were reported by health care professionals.

Of these 8 cases, one was a clinical trial case concerning a female child of unknown age. The event "bullous rash on the face and anterior trunk associated with fever and septicemia" with a fatal outcome was assessed as not suspected to be related to the study medication by the investigator.

Among the remaining seven spontaneous reports, the relevant events reported were Stevens-Johnson syndrome (n=5), Toxic epidermal necrolysis (n=1) and Toxic skin eruption (n=1); in three cases the events were reported with a fatal outcome.

The age group distribution of these seven cases was as follows: two infants (19 months and 2 years), one child (7 years) and four adults (27, 36, 45 and 54 years). Three reports concerned females and four males. The time to onset calculated from the start of the Coartem/Riamet therapy was provided only in four cases and ranged from 2-7 days.

In all of the cases medications which are strongly associated with risk of SJS/TEN were given concomitantly, like: phenobarbital, amoxicillin, paracetamol, sulfamethoxazole-trimethoprim, lopinavir, tenofovir and ritonavir (as part of HIV treatment), allopurinol, methyl dopa,

chloramphenicol, ibuprofen and captopril. In one of these cases, the concomitant medication (amoxicillin and paracetamol) was started on the same day as Coartem. In all of the remaining cases, the exact start and end dates for the co-medications were not provided. In two cases with multiple co-medications, SJS was reported in the medical history with the possibility that the reported event occurred in the context of drug re-challenge. Some of the cases were also poorly documented with not much information provided for a proper assessment.

Literature

Cumulative review identified the below relevant publication:

[Matthew O et al 2013], compared the treatment outcome among patients treated with artesunate/amodiaquine to those treated with artemether-lumefantrine for acute uncomplicated malaria. One case of Steven Johnson-like reaction was observed with artemether-lumefantrine in the study starting on the third day, after completion of therapy. This was adequately treated at the centre and no other complaint was received from the patient.

Comment: No further details were provided about concomitant drugs and the authors have reported only SJS-like reaction.

Discussion and Conclusion

The review revealed that in all cases, there were alternative explanations in the form of additional suspect or concomitant medications which are strongly associated with the risk of severe skin reactions. Some cases contained limited information, which precluded adequate assessment.

The reporting frequency with Coartem/Riamet is 0.01 case per million PTY that is far below the reported incidences in the general population (1.4 to 12.7 cases per million PTY) even when considering underreporting or ethnic differences.

In conclusion, in line with the PRAC conclusions, Novartis believes that the current data does not warrant for a change of the relevant product information and will continue close monitoring the safety topic in the frame of the PSURs.

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Quetiapine and valproic acid interactions: signal strengthening

Daniele Sartori, Uppsala Monitoring Centre and Prof. Alfonso Carvajal, Spain

Summary

The co-administration of quetiapine and valproic acid is a relatively unexplored option for the acute and maintenance treatment of bipolar disorder. According to the European Union Summary of Product Characteristics, the two drugs are known to interact but the co-treatment is "well tolerated". Despite the limited clinical significance of the interaction, some have advised therapeutic drug monitoring. In December 2016, VigiBase, the WHO global database of individual case safety reports, held over 1500 reports of quetiapine and valproic acid as co-suspect or interacting. Five MedDRA preferred terms: blood creatine phosphokinase increased, coma, depressed level of consciousness, disorientation and rhabdomyolysis were selected through shrinkage odds ratios. The resulting series of 20 cases was assessed: at least six cases had been reported in the literature, there were more male than female rhabdomyolysis patients (4:1), and quetiapine raised plasma concentrations hinted at a valproic acid-mediated pharmacokinetic interaction. Most cases (15/20) were reported as serious, and therefore, despite confounding by neuroleptic malignant syndrome and the potential for genetic polymorphisms, the evidence presented may justify an update to the current safety understanding of the two medicines.

Introduction

Quetiapine is an atypical antipsychotic, with antagonistic activity for serotonin 5-HT_{1A}/5-HT₂, dopamine D₁/D₂, histamine H₁ and noradrenaline α₁ and α₂ receptors. It is indicated for schizophrenia, bipolar disorder I, and as add-on treatment for major depressive disorder. Valproic acid is an antiepileptic, thought to increase gamma aminobutyric acid concentrations in the brain.^{1,2}

In the United States (US) and Europe, quetiapine and valproic acid together are licensed for the

treatment of acute moderate to severe manic episodes in bipolar disorder and as maintenance treatment of bipolar disorder (prevention of a manic, mixed or depressive episode) in adults.^{1,2} Limited evidence shows that co-administration of quetiapine and valproic acid in bipolar disorder is more effective than use on their own, both for acute symptoms and maintenance.³⁻⁶ Relatively high co-prescription as opposed to monotherapy emphasizes the need for better understanding of the efficacy of antipsychotics, including quetiapine, in conjunction with lithium, lamotrigine or valproic acid, contrasting.⁷

Recommended doses of quetiapine in adjunct to valproic acid, for both acute and maintenance bipolar disorder treatment, are 400-800 mg per day. Immediate release quetiapine is initiated at 100 mg per day in manic episodes and may be increased up to 800 mg/day over six days, with increments no higher than 200 mg/day. For extended release: 300 mg/day for the first two days, with 400-800 mg/day by day three. Valproic acid doses in mania are mostly documented as monotherapy at 600-750 mg/day. The dose should be increased by 200 mg/day every three days, up to a total of 2500 mg/day in uncontrolled mania.^{8,9}

The polymorphic nature of psychotic disorders poses a challenge to standard posology recommendations or specific combination treatments. Off-label use is common in psychiatry, to explore treatments to which each patient responds most favourably.

Literature and Labelling

The European Union Summary of Product Characteristics (EU SmPC) for quetiapine mentions an increased risk of antipsychotic-

induced side effects when valproic acid is co-administered, but adds that the combination of quetiapine and valproic acid was well tolerated. The US Food and Drug Administration label cites an Astra Zeneca sponsored study from 2007, which found that adding 1000 mg/day of divalproex, a valproic acid formulation, to 300 mg/day of quetiapine produced a 17% mean increase in maximum plasma quetiapine concentration at steady state. At the same daily doses, valproic acid maximum plasma concentration at steady state was found to be reduced by 10-12%.¹⁰ Conversely, a smaller study showed an increase in up to 77% of plasma quetiapine concentrations, when given together with valproic acid.¹¹ Rhabdomyolysis, creatine phosphokinase (CPK) increase and coma (including hyperglycaemic coma) are on the EU SmPC for quetiapine, while the valproic acid EU SmPC includes hyperammonemic coma and consciousness clouding.

Stockley's Drug Interactions describe the evidence on a pharmacokinetic interaction between quetiapine and valproic acid as "limited", adding that the two do not appear to alter each other's exposure. Based on the evidence considered, dose adjustments are not deemed necessary in concurrent use.¹²

The literature reveals several serious cases on concurrent quetiapine and valproic acid use, describing musculoskeletal and neuropsychiatric suspected adverse reactions attributed to one of the drugs or to interaction between the two. Six cases presented here were published and reported to VigiBase, the WHO global database of individual case safety reports (ICSRs).

A 26-year-old male, with a history of CPK increases under quetiapine, was reported to have CPK-raised blood levels under quetiapine/valproic acid. After the valproic treatment was stopped due to a suspicion of hepatic toxicity and the quetiapine dose was doubled, the patient complained of myalgia accompanied by increased CPK. From this, quetiapine was thought to have caused the reaction.¹³ An 85-year-old female treated for four days with quetiapine and valproic acid was found to have CPK increase. The authors did not exclude the possibility of an interaction with pipamperone, nor a pharmacodynamic one with subtherapeutic quetiapine.¹⁴ Rhabdomyolysis and increased CPK were also described in a 37-year-old male who complained of neck muscles stiffness and malaise. The authors postulated a pharmacokinetic interaction between valproic acid and quetiapine had resulted in the inhibition of CYP3A4, one of quetiapine's main metabolic pathways.¹⁵

A 66-year-old patient experienced depressed level of consciousness and reversible parkinsonism due to a suspected pharmacokinetic interaction between quetiapine and valproic acid. The symptoms appeared after the quetiapine dose had

recently been increased to the maximum daily dose of 800 mg, but quetiapine plasma levels were not measured.¹⁶ A 19-year-old patient affected by Batten disease (neuronal ceroid lipofuscinosis – a rare genetic disorder), fell into a hyperammonemic coma three weeks after valproic acid treatment was added to quetiapine 200 mg/day. The patient recovered after valproic acid discontinuation, but the authors did not suspect an interaction.¹⁷ In another case quetiapine was suspected of having promoted a hyperosmolar-hyperglycaemic coma in the presence of valproic acid.¹⁸ An increased exposure to quetiapine due to valproic acid may have occurred, but both drugs have the potential to trigger this condition.

Reports in VigiBase

As of December 2016 there were 1522 ICSRs of quetiapine and valproic acid, co-reported as suspected or interacting, in VigiBase. During a signal detection screening focusing on drug-drug-interactions, 50 quetiapine-valproic acid-interaction combinations were highlighted.

To limit the cases to a number manageable for manual assessment, we performed an automatic case series features comparison using shrinkage odds ratios (see *vigiPoint*¹⁹). Five MedDRA preferred terms (PTs) were identified as relevant and selected: blood creatine phosphokinase increased, coma, depressed level of consciousness, disorientation and rhabdomyolysis. Suicide attempts were excluded, along with cases which contained over three co-suspects, to minimize polypharmacy confounding. Twenty cases remained; the full results of the analysis are available upon request.

The 20 reports originated from the United States (5 cases), Germany (4), Switzerland (3), Canada (2), Australia, Denmark, Italy, Turkey, South Korea and Spain (1 case each). Patient sex was mostly male (13 vs 7), with an average age of 49 years. The indication given was: bipolar disorder in seven cases, schizoaffective disorder in two, paranoid schizophrenia in one, psychotic disorder/psychosis in two, depression in two, and patient restraint, Batten disease and posttraumatic stress disorder in one case each. Five cases reported "Blood creatine phosphokinase increased", five "Coma", eight "Depressed level of consciousness", four "Disorientation" and four "Rhabdomyolysis", all at PT level. Most cases (15/20) were reported as serious.

Two groups of reported events can be identified: musculoskeletal and psychiatric. For these two groups, time to onset, de- and re-challenges, and outcomes were

determined for a given reported MedDRA PT. When two events of the same group were in the same report, the more severe of them was selected.

Musculoskeletal reported adverse events

PTs: Rhabdomyolysis/blood creatinine phosphokinase increased

Six cases (1 to 6 in the table), in two of which quetiapine and valproic acid were reported as interacting, and one case which included the term "Drug interaction". The highest dose of Quetiapine per patient ranged from 50-500 mg/day, while the highest for valproic acid was 250-1500 mg/day. Time to onset ranged from 4 days after valproic acid introduction to 75 days (median 11 days). The outcome was recovery in all six patients.

Case 6 features also disorientation, a neuropsychiatric event (see below), but CPK measurements allowed for rhabdomyolysis to be selected as the main term.

Neuropsychiatric reported adverse events

PTs: Depressed level of consciousness/Coma

Twelve cases in total (7 to 18 in the table). In four, quetiapine and valproic acid were reported as interacting. The highest dose of quetiapine per patient ranged from 200-950 mg/day, while the highest for valproic acid was 300-2500 mg/day. Time to onset ranged from 1 day after valproic acid introduction to 16 months (median 17 days). The outcome was recovery in seven patients and unknown with reaction abated in two.

In the narrative of case 7 there is a mention of CPK increase, but the information is incomplete. Therefore, coma was chosen as main term.

PT: Disorientation

Two cases (19 and 20 in the table). Neither reported the two drugs as interacting. The highest dose of Quetiapine per patient ranged from 400-600 mg/day, while the highest for valproic acid was 1.5-500 mg/day (one of which is possibly 1.5 grams due to entry mistake). Time to onset was 17 days and 3 years. The outcome was recovery in both cases.

Discussion

Quetiapine and valproic acid are known to interact as two central nervous system (CNS) depressant agents. The interaction is not thought to be clinically significant and is regarded as "well tolerated", however, therapeutic drug monitoring has been recommended.²⁰ By contrast, most of the assessed cases (15/20) were reported as serious. For rhabdomyolysis and increases in blood CPK, the time to onset is consistent with a drug induced effect, yet the reactions per se could be explained

by concomitant diseases, co-reported terms or co-administered medicines.

The musculoskeletal subgroup contributes with 4 males and 1 female to the uneven sex ratio in the case series (13 males and 7 females). Fat-to-muscle ratio differences between sexes can account for rhabdomyolysis. Other alternative explanations include: potentially undiagnosed glycolysis, glycogenolysis, and pentose phosphate pathways enzymatic polymorphism, mitochondrial toxicity and calcium homeostasis dysregulation.²¹

Additionally, rhabdomyolysis is part of the neuroleptic malignant syndrome (NMS) clinical presentation, which is known to be more frequent in men.²² In case 4, a quetiapine-valproate pharmacokinetic interaction was suspected to have induced rhabdomyolysis as part of an abortive NMS form. The patient's symptoms began with neck stiffness, which resembles a cervical dystonia literature case, suspected to have been a pharmacokinetic interaction between quetiapine and valproic acid.²³ Cases 5 and 6 are confounded by respiratory infection and NMS respectively. In case 1, the reporter concluded that the patient was predisposed to valproic acid hepatotoxicity on the basis of repeated positive rechallenges, and that quetiapine was responsible for the CPK increase. After withdrawal of valproate, the patient recovered from hepatic complications, after quetiapine dechallenge his CPK went back to normal. Reiche et al. (case 2) suggest a blood CPK increase caused by valproic acid resulting from prolonged clearance due to interaction with concomitant pipamperone. They do not, however, exclude the possibility of a pharmacodynamic interaction between valproic acid and quetiapine, adding that quetiapine was below therapeutic levels at admission to hospital.

Accounting for potential confounders in the neuropsychiatric group, consciousness fluctuations and coma are also symptoms of NMS. In case 7, marked increases of antipsychotic plasma levels due to pharmacokinetic interaction could have induced NMS. Alternatively, valproic acid encephalopathy can also reasonably explain decreased consciousness and coma. Valproic acid metabolites can inhibit the urea cycle and cause hyperammonemia, as in case 17.¹⁷ Wu et al. (case 18) suggest that the patient's hyperglycaemic coma was promoted by high dose quetiapine and possibly complicated by valproic acid co-administration, but worsened by high sugar consumption. Cases which did not co-report any of the above discussed conditions are 9 and 10, both describing a decrease in consciousness. Both could be quetiapine dose-related: the first reports a

prescribed overdose, and the second an unintentional four-fold overdose due to lack of patient adherence. Some cases list extrapyramidal symptoms, a known side effect of antipsychotics. Case 12 reports pseudoparkinsonism induced by increased plasma levels of quetiapine. Similarly, case 13 lists parkinsonism and depressed consciousness, attributed to a pharmacokinetic interaction leading to increased quetiapine plasma levels and a recovery after dose reduction. In another patient (case 11), depressed consciousness co-occurred with gait disturbances and around the same time of a quetiapine dose increase. The reported off-label indication was depression, and the incremental dosing occurred according to the label. In case 8, extrapyramidal symptoms and depressed level of consciousness are co-reported after quetiapine dose increase. Quetiapine overdose leads to CNS depression and increased plasma levels due to pharmacokinetic interactions can have the same effect.

In addition to polytherapy-induced interactions, smoking, alcohol, and drug abuse are prevalent in patients affected by psychotic disorders.²⁴ Quetiapine pharmacokinetics do not seem to be altered by smoking. Nicotine however, is metabolized by CYP2A6, the same cytochrome which hydroxylates valproic acid.^{25,26} These considerations are applicable to case 7, a smoker. Smoker status, alcohol or substance abuse could have been unreported in the rest of the case series.

Conclusion

The potential for quetiapine-valproic acid interactions has been extensively described in the literature, with at least six case reports published in journals. The assessed case series features musculoskeletal and psychiatric events that occurred after dose increases of quetiapine, or where the reporter suspected a pharmacokinetic interaction. Bearing reported confounders in mind, such as NMS, or individual predisposing factors, current information could still be considered for updating. In particular, the co-administration of quetiapine and valproic acid is regarded as well tolerated, yet 15 out of 20 cases were serious. While psychiatrists and clinical pharmacologists might be aware of the events described here, general practitioners might not be, stressing the relevance of strengthening the safety understanding and available documentation on the two medicines.

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Table 1. Overview of selected case reports of blood creatine phosphokinase increased, coma, depressed level of consciousness, disorientation and rhabdomyolysis in association with quetiapine (Q) and valproic acid (VA) in VigiBase

Case	Serious	Age/Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Q/VA dose	Reactions (MedDRA terms, main event in bold)	Time to onset	Dechallenge/Rechallenge	Outcome	Comments
1	Y	26/M	Q, VA (both S) Lithium (C)	200 mg/day 400 mg/day after valproate stopped 1500 mg/day	Blood creatine phosphokinase increased , creatine kinase MB increased, hepatic enzymes increased	11 days	Q: Dechallenge positive VA: Dechallenge positive	Recovered	Literature reference: Erdogan et al. VA levels: 50 mg/l, thyroid function normal. AST, ALT, LDH elevation linked to VA, while CPK and CPK-MB increase to Q. History of hepatic enzyme increases while on VA and CPK increase on Q. VA withdrawn first, with lowering of hepatic enzymes. Followed by increase in CPK after Q dose was raised to 400 mg/day. Q then discontinued and CPK values back to normal.
2	Y	85/F	Q, VA, pipamperone (all S) Acetylsalicylic acid, levothyroxine, nifedipine, torasemide, furosemide (all C)	200 mg/day/600 mg/day	Drug clearance decreased, drug interaction, myopathy, blood creatine phosphokinase increased , muscle pain, muscle weakness, myoglobin blood increased	4 days after VA introduction	Q: Dechallenge positive/ Rechallenge negative VA: Dechallenge positive	Recovered	Literature reference: Reiche et al. Suspected interaction between VA and pipamperone as well as between VA and Q. Q levels below therapeutic: 25 ng/ml (reference 70-170 ng/ml), VA levels within therapeutic range: 46 mcg/ml (reference 30-100 mcg/ml).
3	-	27/M	Q, VA, venlafaxine (all S)	200 mg/day/250 mg/day	Rhabdomyolysis , muscle pain, creatine kinase increased	-	-/-	Recovered	-
4	Y	37/M	Q (I), VA (S)	500 mg/day 1000 mg/day	Rhabdomyolysis , muscle pain, musculoskeletal stiffness, muscle rigidity, muscle weakness, malaise, creatine kinase increased, body temperature increased, drug interaction	2.5 months	Q: Dechallenge positive VA: Dose not changed	Recovered	Literature reference: Jahn et al. Suspect of abortive neuroleptic malignant syndrome with fever (37.9 C), tremor in extremities. VA 82.4 mg/l.
5	Y	54/M	Q, VA, paliperidone (all S) Paroxetine, flurazepam, delorazepam (all C)	50 mg/day 1000 mg/day	Bronchopneumonia, rhabdomyolysis , renal failure acute	2 months	Q: Dechallenge positive VA: Dechallenge positive	Recovered	-
6	Y	64/M	Q, VA (both I) Indapamide, hydrochlorothiazide/lisinopril, amlodipine (all C)	50 mg/day titrated to 100 mg/day over 1 day 300 mg/day	Neuroleptic malignant syndrome, rhabdomyolysis , renal failure acute, acidosis metabolic, hypotension, extrapyramidal disorder, fever, disorientation	4 days	Q: -/ VA: Dechallenge positive	Recovered	-
7	Y	65/M	Q, VA, pipamperone (all S)	Titrated from 100 mg to 950 mg/day in 17 days 150 mg titrated to 300 mg in 1 day	Neuroleptic malignant syndrome, tremor, rigors, muscle spasticity, depressed level of consciousness , fever, confusion, dysarthria	1 month	Q: Dechallenge positive VA: Dose not changed	Recovered	Q above studied doses. Mental disorders due to brain damage. Chronic obstructive pulmonary disease, smoker, fever 38.1 C. Q plasma concentration: 3498 nmol/l (reference 183-442 nmol/l) 1 day after withdrawal. C-reactive protein: 83 mg/l. Pipamperone was taken for 9 days, in overlap with Q/VA.
8	Y	66/M	Q, VA (both I), lithium (S) Ceftriaxone, metronidazole, heparin (all C)	200 mg/day 1500 mg/day Quetiapine up to 500 mg/day after surgery	Depressed level of consciousness , extrapyramidal disorder, diabetes insipidus, hypematraemia	3 days after surgery Several years of treatment with both medicines	Q: Dechallenge positive/ Reintroduced at lower dose without reaction VA: Dechallenge positive/ Rechallenge negative	Recovered	Acute cholecystitis. Developed reactions after surgery, lithium-induced diabetes insipidus pre-existing, hypematraemia due to decreased consciousness and subsequent reduced liquids intake. Recent increase of Q.
9	Y	56/M	Q, VA, perazine (all S) Acetylsalicylic acid, clopidogrel, hydrochlorothiazide/valsartan, ramipril, pantoprazole (all C)	100 mg/day titrated to 900 mg/day over 1 month 300 mg/day	Depressed level of consciousness , consciousness decreased, drug interaction, restlessness, prescribed overdose	1 day after valproate introduction	Q: Dose reduced VA: Dose reduced	Recovered	Q above studied doses. Q at 191 ng/ml (reference 70-170 ng/ml). VA at 11.2 mcg/ml (reference 50-100 mcg/ml). Reactions occurred at the day of peak Q concentration. VA was introduced the same day. Perazine cannot be excluded, but was introduced five days before valproate.

SIGNAL

Case	Serious	Age/Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Q/VA dose	Reactions (MedDRA terms, main event in bold)	Time to onset	Dechallenge/Rechallenge	Outcome	Comments
10	Y	39/F	Q, VA (both S)	200 mg/day 1000 mg/day	Affect lability, depressed level of consciousness , inappropriate schedule of drug administration, pneumonia, pyrexia, somnolence, treatment noncompliance	5 days (after hospitalization and treatment re-start)	Q: Dechallenge positive VA: Dechallenge positive	-	Hospitalized due to fever and suspected pneumonia, treated with levofloxacin. Antipsychotic regimen had not been taken by patient and was started during hospital stay.
11	Y	54/F	Q, VA (both S)	50 mg/day titrated to 400 mg/day over 12 days 700 mg/day	Depressed level of consciousness , gait disturbance, overdose, pain, physical assault, speech disorder	12 days	Q: -/Rechallenge positive VA: Dechallenge positive	-	The overdose was not intentional but reported by the patient as she considered her physician to be overdosing her.
12	Y	66/F	Q, VA (both I)	300 mg/day titrated to 800 mg/day over follow-ups 1000 mg/day titrated up to 1500 mg/day over follow-ups	Hemiparesis, depressed level of consciousness , parkinsonism, temporal disorientation, memory deficit, cognitive deterioration	17 days	Q: Dechallenge positive VA: Dechallenge unknown	Recovered	Literature reference: De Dios et al. Cortical-subcortical atrophy. VA: 78 mg/l after events.
13	Y	74/M	Q, VA, aripiprazole (all I) Finasteride, alfuzosin, lithium (all C)	50 mg/day titrated to 500 mg/day in 19 days 1600 mg/day brought to 2400 mg/day after 9 days	Drug interaction, depressed level of consciousness, parkinsonism, coma , blood thyroid stimulating hormone decreased, altered state of consciousness	19 days after Q introduction	Q: Dose reduced VA: Dose reduced	Recovered	History: benign prostatic hyperplasia, lacunar infarction, nervous system disorder NOS, cerebral degeneration, emergency care, hospitalization, chronic kidney disease. Q was added on VA and lithium. VA dose brought up from 900 mg per day to 1600 mg per day on the day Q was started. Q: 283 mcg/l (reference: 70-170 mcg/l); VA within therapeutic levels; aripiprazole below therapeutic levels.
14	Y	-/M	Q, VA, lorazepam (all S)	"high doses" of both drugs	Dehydration, depressed level of consciousness, coma	-	-/-	-	-
15	-	-/F	Q, VA, sertraline (all S)	-	Convulsions, coma	-	-/-	-	-
16	-	57/F	Q, VA, nifedipine (all S)	-	Hypotension, coma	-	-/-	-	-
17	Y	19/M	Q, VA, oxcarbazepine (all S)	200 mg/day 1000 mg/day	Anticonvulsant drug level above therapeutic, coma , hyperammonemic encephalopathy, hyperammonemia, drowsiness	3 weeks after VA introduction	Q: -/ VA: Dechallenge positive	Recovered	Literature reference: Erling et al. Hyperammonemic coma due to VA. VA: 756 mcg/l (no reference provided but above therapeutic).
18	Y	39/M	Q, VA (both I), lorazepam (S)	700-800 mg/day 2500 mg/day	Hyperosmolar state, hypercapnia, lipids increased, hypoxia, diabetes mellitus, coma , blood cholesterol increased, drug interaction, hypertriglyceridemia, hyperglycaemia, diabetic ketoacidosis, weight increased	16 months	Q: Dechallenge positive VA: Dose not changed	Recovered	Literature reference: Wu et al. Coma/depressed consciousness due to hyperglycaemia (high-sugar dieting habits). Patient without history of diabetes.
19	N	38/F	Q, VA, lithium (all S)	600 mg/day 500 mg/day	Disorientation	17 days	Q: Dose reduced VA: Dechallenge positive	Recovered	VA introduced after 11 days of Q use. Q can increase plasma concentration of lithium.
20	-	21/M	Q, VA, fluvoxamine (all S)	400 mg/day 1.5 mg/day	Thinking abnormal, concentration impaired, disorientation , dizziness, nausea	3 years	-/-	Recovered	Possible error in reporting VA dose (mg instead of grams).

Enhancing Pharmacovigilance in Low and Middle Income Countries using Smart Safety Surveillance

Access to priority medicines and vaccines in low and middle-income countries (LMICs) has improved significantly in the last few years. With the urgent need for novel treatments for diseases such as tuberculosis, malaria and HIV, more and more medicinal products are expected to be released on an accelerated, fast-track basis. However, there has not been a proportionate improvement in pharmacovigilance (PV). This is of great concern, as effective safety monitoring systems are essential to learn about the safety of novel treatments, manage adverse effects and minimize risks. In addition, a lack of functional PV system is a barrier to access as many new products require safety monitoring as a condition to authorization of a license for use.



Bedaquiline stock in a hospital in Kyrgyzstan

In 2016, the World Health Organization, (WHO) in collaboration with the Bill and Melinda Gates Foundation (BMGF) launched the Smart Safety Surveillance or Project 3S to help LMICs identify, assess and adequately manage the risks associated with new medicines and vaccines. The 3S approach proposes strengthening of PV systems and practices in LMICs, to support the introduction of new health products through identification, assessment, and management of any risks associated with them. Although the 3S approach was borne out of a WHO-BMGF grant agreement, the approach is equally valid for strengthening PV systems in countries supported by other donors such as UNITAID.

One of the products that will be used as a pathfinder to test the concept of the 3S approach is bedaquiline. Bedaquiline (BDQ), is a new class of medicines against M. Tuberculosis indicated for the use of multi-drug resistant tuberculosis (MDR-TB). The emergence of drug-resistant tuberculosis (TB) is a major threat to global TB care and control, and even more so when there is resistance to multiple drugs. Bedaquiline was approved for use in the treatment of MDR-TB under the United States Food and Drug Administration (U.S FDA) accelerated-approval regulations and conditional under the European Medicines Agency (EMA). Subsequently, the World Health Organization (WHO) issued conditional recommendations for its use through an interim policy guidance published in 2013. One of the conditional requirements is pharmacovigilance and proper management of adverse drug reactions and prevention of drug-drug interactions. So far, WHO estimates that bedaquiline has been introduced and used in over 46 countries worldwide, under various mechanisms of compassionate use, expanded access programmes, donation programmes, import waiver and registered market access.



All partners around the table to discuss PV needs in Armenia

Armenia and Kyrgyzstan are among 27 countries in the world with a high burden of multidrug-resistant tuberculosis (MDR-TB) and among the 18 high-priority countries for TB in the WHO European Region. In March 2018, representatives from WHO Safety and Vigilance team at Headquarters in Geneva, WHO regional office in Europe, and WHO country offices in Armenia and Kyrgyzstan visited TB clinics and national PV centres in Armenia and Kyrgyzstan to gain insight on existing PV systems and explore how the 3S principles can be applied to strengthen existing systems.



Hospital Staff in a TB hospital in Kyrgyzstan

Through various meetings and discussions, WHO has gained an understanding of structural components such as legislations, existence of guidelines and standard operating procedures, human resources and access to information, in both countries. The team also gained a good understanding of the reporting process, analysis and level of decision making was also acquired. WHO representatives also met with a few non-governmental agencies such as Médecins for sans Frontières (MSF) and KNCV to clarify roles, activities and future plans under the scope of PV. The team gathered information on areas of PV that require support, so that countries are prepared for the safety monitoring of new medicinal products. WHO, together with the countries, and other partners such as the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK is designing a work plan to address identified gaps and needs, with the aim of strengthening the PV systems in countries.