

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:

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

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

This newsletter also includes update on pharmacovigilance strengthening activities in Ethiopia.

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Alemtuzumab

Risk of serious cardiovascular and immune-mediated adverse reactions

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the use of alemtuzumab (Lemtrada®) will be restricted due to the risk of serious cardiovascular and immune-mediated adverse drug reactions. Strengthened requirements for monitoring alemtuzumab have been introduced in addition to an urgent safety review conducted by the EU.

Alemtuzumab is a monoclonal antibody indicated for the treatment of adults with relapsing-remitting multiple sclerosis.

Alemtuzumab should only be started in new patients with either: highly active relapsing-remitting multiple sclerosis if all other disease-modifying therapies are contraindicated; or relapsing-remitting multiple sclerosis that is highly active despite an adequate course of treatment with at least two other disease-modifying therapies. Patients already on alemtuzumab may continue treatment if beneficial and they have discussed the additional monitoring requirements with a health-care professional.

New monitoring requirements and precautions for use include: monitoring vital signs (e.g. blood pressure) before and periodically during alemtuzumab infusion, monitoring liver function tests and immediate evaluation of patients who develop early manifestations of pathologic immune activation.

Patients should be alerted of symptoms of: pulmonary haemorrhage, myocardial infarction, stroke, hepatic injury and haemophagocytic lymphohistiocytosis.

Reference:
Drug Safety Update, MHRA,

17 May 2019 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.3, 2019: Cardiovascular and immune-mediated adverse effects in Europe)

Avelumab

Risk of pancreatitis

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for avelumab (Bavencio®) will be revised to include pancreatitis as an adverse drug reaction.

Avelumab is indicated for unresectable Merkel cell carcinoma.

Cases of pancreatitis have been reported in patients treated with avelumab overseas. Although no corresponding cases have been reported in Japan, the MHLW and the PMDA have concluded that the revision of the package insert was necessary based on their investigation of the currently available evidence and because there have been no findings to indicate ethnic differences in the pharmacokinetics and safety profile of the medicine between Japanese and overseas patients.

Reference:
Revision of Precautions, MHLW/PMDA, 4 June 2019 (www.pmda.go.jp/english/)

Baloxavir marboxil

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for baloxavir marboxil (Xofluza®) will be revised to include shock and anaphylaxis as adverse drug reactions.

Baloxavir marboxil is indicated for influenza A or B viral

infections. Baloxavir marboxil inhibits the synthesis of viral RNAs.

A total of 42 cases involving shock or anaphylaxis have been reported in Japan during the previous three fiscal years. For 16 cases, a causal relationship between the drug and event could not be excluded. Additionally, one of the cases was fatal.

The MHLW and PMDA have concluded that revision of the package insert is necessary based on the results of their investigation of the currently available evidence and in consultation with expert advisors.

Reference:
Revision of Precautions, MHLW/PMDA, 4 June 2019 (www.pmda.go.jp/english/)

Cedar pollen extract powder, *dermatophagoides* extract bulk powder

Risk of anaphylaxis

Japan. The MHLW and the PMDA have announced that the package inserts for cedar pollen extract (e.g. Cedartolen Japanese cedar pollen sublingual drop®) and *dermatophagoides* extract bulk powder (e.g. Actair house dust mite sublingual tablets®) will include anaphylaxis as an adverse drug reaction.

Cedar pollen extract is indicated for cedar pollinosis as desensitization therapy and *dermatophagoides* extract bulk powder is indicated for desensitization therapy against allergic rhinitis caused by mite antigens.

Patients should be alerted for the onset of anaphylaxis particularly when engaged in intense exercise, alcohol consumption or bathing. The reaction can take two or more

hours to occur following administration of the extracts.

Two cases of anaphylaxis have been reported in Japan during the previous three fiscal years. The reaction occurred after exercise or bathing within two or more hours after the cedar pollen extract was taken. Additionally, two cases of anaphylaxis have been reported with the use of *dermatophagoides* extract bulk powder. No patient mortalities have been reported.

Reference:

Revision of Precautions, MHLW/PMDA, 9 July 2019 (www.pmda.go.jp/english/)

Codeine, dihydrocodeine, tramadol

Contraindication in children: Risk of serious respiratory depression

Japan. The MHLW and the PMDA have announced that the package inserts for products containing codeine, dihydrocodeine or tramadol should be revised to include contraindications in children under 12 years of age (for all uses), and patients under 18 years of age when used for pain relief after tonsillectomy or adenoidectomy, due to the risk of serious respiratory depression.

Codeine, dihydrocodeine and tramadol are indicated to relieve coughs and pains.

Following the announcement of the US Food and Drug Administration (FDA) in 2017 of the contraindication of products containing codeine, dihydrocodeine or tramadol in children under 12 years, MHLW and PMDA have reviewed available safety information and concluded that the revision of package inserts is necessary.

In Japan there are four reports of morphine like toxic symptoms such as respiratory depression in patients using codeine, dihydrocodeine or tramadol. Mortality has not been reported.

Reference:

Revision of Precautions, MHLW/PMDA, 9 July 2019 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.1, 2018: Limited use: Only for adults of 18 years of age and older in USA; No.6, 2017: Contraindication in children and ultra-rapid metabolisers in Australia; No.4, 2017: Cautions against use in children and teenagers under 18 years of age in Japan)

Epoprostenol

Risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced that the package insert for epoprostenol (Flolan®) should be revised to include thrombocytopenia as an adverse drug reaction.

Epoprostenol is indicated for pulmonary arterial hypertension.

A total of 18 cases of thrombocytopenia have been reported in Japan during the previous three fiscal years. For three cases, a causal relationship between the drug and event could not be excluded.

Patients should be monitored carefully and should have periodic laboratory tests. If any abnormalities are observed, dose reduction, discontinuation or other appropriate measures should be taken.

Reference:

Revision of Precautions, MHLW/PMDA, 9 July 2019 (www.pmda.go.jp/english/)

Febuxostat, topiroxostat

Potential risk of cardiovascular death

Japan. The MHLW and the PMDA have announced that the package inserts for febuxostat (Feburic®) and topiroxostat (Uriadec®) should be revised to warn about the potential risk of cardiovascular death in patients with cardiovascular disease.

Febuxostat and topiroxostat are indicated for gout or hyperuricemia.

The PMDA investigated studies conducted overseas. In the US, the CARES study showed a higher risk of cardiovascular death in the study group treated with febuxostat compared to the control group treated with allopurinol. The FDA restricted the use of febuxostat and revised the package insert in February 2019 to provide an alert on cardiovascular deaths.

The European Medicines Agency (EMA) required the marketing authorization holder of febuxostat to conduct a clinical study (FAST study) to assess the cardiovascular risks of febuxostat in patients with gout who had a cardiac disease. The FAST study is ongoing.

In Japan, clinical trials do not show evidence of a higher incidence of cardiovascular events in the febuxostat study group compared to the control groups (placebo group or allopurinol group).

However, considering the evidence from studies conducted overseas and available evidence in the literature, PMDA has concluded that it is appropriate to add the CARES study results concerning cardiovascular death to package insert. Although no concerns were expressed about cardiovascular risks in a similar drug with a xanthine oxidase inhibitory effect, topiroxostat, it is

considered appropriate to add the same precautions to the package insert of topiroxostat.

Reference:

Revision of Precautions, MHLW/PMDA, 9 July 2019 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.9, 2019: Increased risk of death in USA; No.6, 2017: Potential risk of heart-related death in USA; No.3, 2016: Risk of heart failure in Canada)

Fenspiride

Withdrawal due to the risk of heart rhythm problems

Europe. The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the marketing authorizations for cough medicines containing fenspiride (Elofen®, Epistat®, Eurefin®) should be revoked, due to the risk of heart rhythm problems.

Fenspiride is used to relieve cough resulting from lung diseases in adults and children of two years and older.

The PRAC considered all available evidence from cases of QT prolongation and torsades de pointes in patients using fenspiride. Heart rhythm problems can be serious, occur suddenly, and it is not always possible to identify patients at risk in advance. The use of fenspiride for treatment of cough is considered to be non-serious, and therefore the PRAC recommends that fenspiride should no longer be marketed.

Reference:

EMA, 17 May 2019 (www.ema.europa.eu)

(See WHO Pharmaceuticals Newsletter No.3, 2019: Potential risk of problems with heart rhythm in Europe)

Gentian violet

Risk of cancer

Canada. Health Canada has announced that there is potential evidence of a link between the use of gentian violet and cancer.

Gentian violet is a non-prescription medicine used to treat cutaneous and mucocutaneous infections.

Following a review of the scientific literature and risk assessment on violet containing human therapeutic products, Health Canada concluded that the evidence from animal studies in the scientific literature suggests a potential link between gentian violet and cancer.

The assessments were triggered by a recommendation from the WHO's Codex Alimentarius Commission which advised regulatory authorities to prevent exposure to gentian violet in food due to a potential cause of cancer.

Health Canada notified the manufacturer of gentian violet of the assessment results. The manufacturer agreed to voluntarily discontinue marketing of their product in Canada and the health product drug licence for gentian violet has been cancelled.

Reference:

Summary Safety Review, Health Canada, 12 and 27 June 2019 (www.hc-sc.gc.ca)

Glucagon-like peptide-1 (GLP-1) receptor agonists

Risk of diabetic ketoacidosis

United Kingdom. The MHRA has requested that the Summaries of Product Characteristics and Patient Information Leaflets for Glucagon-like peptide-1 (GLP-1) receptor agonists

(exenatide, liraglutide and dulaglutide) are updated to include advice on reducing insulin dosage using a stepwise approach and monitoring of blood glucose to minimize the risk of diabetic ketoacidosis.

GLP-1 is indicated to treat adults with type-2 diabetes and are not substitutes for insulin.

There have been reports of diabetic ketoacidosis in patients with type-2 diabetes on a combination of a GLP-1 receptor agonist and insulin when the concomitant insulin is rapidly reduced.

An EU review concluded that the reported cases of diabetic ketoacidosis could be attributed to abrupt discontinuation or dose reduction of insulin while initiating GLP-1 receptor agonist therapy, resulting in poor glycaemic control.

Health-care professionals are advised that if the insulin dose is to be reduced, a stepwise approach is recommended. Also, they should monitor for signs and symptoms of diabetic ketoacidosis and risk factors with patients.

Reference:

Drug Safety Update, MHRA, 19 June 2019 (www.gov.uk/mhra)

Magnesium sulfate

Risk of skeletal adverse effects in neonates

United Kingdom. The MHRA has announced that the product information for products containing magnesium sulfate will be updated to warn of skeletal adverse effects observed with administration for more than five to seven days during pregnancy.

Magnesium sulfate is indicated for the prevention of further seizures associated with eclampsia in pregnancy and for the treatment of magnesium deficiency in hypomagnesemia.

In 2013, the US FDA issued a safety recommendation against the use of magnesium sulfate for more than five to seven days when used as a tocolytic (an indication not authorized in the UK). Such prolonged exposure may result in significantly higher cumulative doses than those encountered with use in the UK for eclampsia or foetal neuroprotection.

The MHRA is not aware of any reports in the UK of skeletal adverse effects or relevant biochemical effects in the neonate following use of magnesium sulfate but, considering that there is an increase in the usage in the UK, the decision to update product labels was made, based on the recommendations from the Paediatric Medicines Expert Advisory Group. The MHRA advises health-care professionals to consider monitoring neonates for abnormal calcium and magnesium levels and skeletal adverse effects if maternal treatment with magnesium sulfate is prolonged.

Reference:
Drug Safety Update, MHRA, 17 May 2019 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.6, 2015: Risk of hypermagnesaemia in Japan)

Metformin

Contraindication removed

Japan. The MHLW and the PMDA have announced that the package inserts for products containing metformin (e.g. metformin, Glycoran®; vildagliptin/metformin, EquMet®; pioglitazone/metformin, METACT®) should be revised to remove a previous contraindication in patients with mild renal impairment. Treatment in patients with severe renal impairment is still a contraindication.

Metformin is indicated to treat type-2 diabetes.

There was a concern that patients with renal impairment would be at a higher risk of lactic acidosis because the blood concentration of metformin increases due to a delay in its excretion. Therefore, it was contraindicated in patients with renal impairment including mild impairment.

In recent years, the FDA and the EMA have reviewed published papers and both organizations have concluded that metformin may be used in patients with mild to moderate renal impairment.

The PMDA considered the available information on pharmacokinetics, overseas published literature and guidelines, and concluded that metformin may be safely used in patients with moderate renal impairment if risks are minimized. Also, the package insert should include advice on low dose initiation of treatment, dose adjustments depending on the patient's condition, careful follow-up, and other required precautions in patients with renal impairment.

Reference:
Revision of Precautions, MHLW/PMDA, 18 June 2019 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.3, 2016: Warnings for certain patients with reduced kidney function in USA)

Nivolumab, pembrolizumab

1. Risk of tuberculosis

Japan. The MHLW and the PMDA have announced that the package inserts for nivolumab (Opdivo®) and pembrolizumab (Keytruda®) should be revised to include tuberculosis as an adverse drug reaction.

Nivolumab and pembrolizumab are indicated for cancer

treatment including malignant melanoma, unresectable, advanced or recurrent non-small cell lung cancer and relapsed or refractory classical Hodgkin lymphoma. They are classified as anti-programmed cell death protein-1 (PD-1) antibody medicines.

Cases of tuberculosis have been reported in patients treated with anti-PD-1 antibody medicines in Japan and overseas.

A total of 14 cases involving tuberculosis have been reported in Japan during the previous three fiscal years. For 10 cases, a causal relationship between the drug and the event could not be excluded.

The MHLW and PMDA have concluded that revision of the package insert is necessary based on the results of their investigation of the currently available evidence and in consultation with expert advisors.

Reference:
Revision of Precautions, MHLW/PMDA, 4 June 2019 (www.pmda.go.jp/english/)

2. Risk of enteritis

Japan. The MHLW and the PMDA have announced that the package inserts for nivolumab and pembrolizumab should be revised to include enteritis as an adverse drug reaction.

A total of 10 cases of enteritis, 35 cases of intestinal perforation and 35 cases of ileus have been reported in patients treated with nivolumab or pembrolizumab in Japan during the previous three fiscal years. For seven cases of enteritis, eight cases of intestinal perforation and two cases of ileus, a causal relationship could not be excluded.

Before the revision, colitis and severe diarrhoea were written as adverse drug reactions; but MHLW and PMDA concluded that revision of the package insert is necessary based on

the results of the investigation of the currently available evidence.

Reference:

Revision of Precautions, MHLW/PMDA, 9 July 2019 (www.pmda.go.jp/english/)

Propofol

Potential risk of priapism

Canada. Health Canada has requested that the manufacturers of propofol containing products update the Canadian product safety information to include information on the potential link between propofol containing products and the risk of priapism.

Propofol containing products are used to make a patient relax, calm, sleepy (sedation) or unconscious (anesthesia) during surgery or medical procedures in children and adults.

Priapism is a prolonged, and usually painful, erection of the penis not caused by sexual stimulation. It is a rare, but potentially serious medical condition.

Health Canada had received one Canadian report of priapism related to the use of propofol-containing products. A review of this report found a possible link between the drug and priapism.

Reference:

Summary Safety Review, Health Canada, 12 July 2019 (www.hc-sc.gc.ca)

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Risk of Fournier's gangrene

Egypt. The Egyptian Pharmaceutical Vigilance Center (EPVC) has announced

that the product information for sodium-glucose co-transporter 2 (SGLT2) inhibitors will be revised to include a warning of the risk of Fournier's gangrene.

Cases of Fournier's gangrene (necrotising fasciitis of the perineum) have been reported with the use of SGLT2 inhibitors.

SGLT2 inhibitors are indicated for the treatment of type-2 diabetes. Medicines registered in Egypt include dapagliflozin, canagliflozin and empagliflozin.

Fournier's gangrene is a rare but serious and potentially life-threatening infection that occurs mostly in men. Patients should be advised to seek urgent medical attention if they experience severe pain, tenderness, erythema or swelling in genital or perineal area accompanied by fever or malaise. If Fournier's gangrene is suspected, the SGLT2 inhibitor should be stopped and treatment started promptly.

Reference:

Newsletter, EPVC, May 2019 (www.epvc.gov.eg)

(See WHO Pharmaceuticals Newsletter No.3, 2019: Risk of necrotising fasciitis of the perineum (Fournier's gangrene) in Singapore and in Japan; No.2, 2019: Risk of Fournier's gangrene in UK; No.5, 2018: Risk of serious infection of the genital area in USA)

Tofacitinib

Risk of pulmonary embolism

1. Europe. The EMA's PRAC has recommended, as a temporary measure, that doctors must not prescribe the 10 mg twice-daily dose of tofacitinib (Xeljanz®) in patients who are at high risk of blood clots in the lungs (e.g. patients who have heart failure, cancer, inherited blood clotting disorders or a history of blood clots) due to the risk of pulmonary embolism and overall mortality.

Tofacitinib is an oral, immunomodulatory disease-modifying anti-rheumatic medicine, indicated for the treatment of rheumatoid arthritis, psoriatic arthritis and severe ulcerative colitis.

The PRAC's recommendation follows results from an ongoing study, which showed an increased risk of blood clots in the lungs and death with 19 cases of pulmonary embolism when the 10 mg twice daily dose was used. This is double the recommended dose for rheumatoid arthritis. Once the review is concluded, updated guidance will be provided to patients and health-care professionals.

Patients are advised not to stop or change their dose of tofacitinib without talking to their doctor. Patients receiving tofacitinib, irrespective of the indication, should be monitored for the signs and symptoms of pulmonary embolism.

Reference:

EMA, 17 May 2019 (www.ema.europa.eu)

2. United Kingdom. The MHRA has announced that a new contraindication for use of tofacitinib has been introduced. The 10 mg twice-daily dose or tofacitinib must not be used in patients at high risk of pulmonary embolism.

Patients already being treated with the 10 mg twice-daily dose of tofacitinib who are at high risk of pulmonary embolism should be switched to alternative treatments.

Reference:

Drug Safety Update, MHRA, 17 May 2019 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.3, 2019: Increased risk of blood clots in lungs and death in Europe; No.2, 2019: Increased risk of blood clots in the lungs and death in USA)

Triptans

Risk of headaches due to medication overuse

Japan. The MHLW and the PMDA have announced that the package inserts for triptans such as sumatriptan (Imigran®), naratriptan (Amerge®), eletriptan (Relpax®), zolmitriptan (Zomig®) and rizatriptan (Maxalt®) should be revised to include headache caused by medication overuse as an adverse drug reaction.

Triptans are indicated for treatment of migraine.

Six cases of headaches due to medication overuse have been reported in Japan during the previous three fiscal years. For all of the six cases, a causal relationship between the drug and event could not be excluded.

Although only a small number of cases of headaches due to medication overuse have been reported in patients treated with triptans in Japan, the MHLW and PMDA have concluded that revision of the package insert is necessary based on the results of the investigation of the currently available evidence and in consultation with expert advisors.

Reference:

Revision of Precautions,
MHLW/PMDA, 4 June 2019
(www.pmda.go.jp/english/)

Cyproterone

Risk of meningioma

Europe. The EMA's PRAC has started a review of cyproterone (e.g. Androcur®) which will investigate the risk of meningioma, a rare, usually non-malignant tumour of the membranes covering the brain and spinal cord.

Cyproterone is a steroidal antiandrogen, indicated for the treatment of a range of conditions, including excessive hair growth, prostate cancer, acne, and in hormone replacement therapy.

A recent study in France suggested a risk of meningioma with cyproterone use. The PRAC will examine available evidence and make recommendations.

Reference:

EMA, 11 July 2019
(www.ema.europa.eu)

Ipilimumab, nivolumab

Potential risk of hemophagocytic lymphohistiocytosis (HLH)

Canada. Health Canada will work with the manufacturers of ipilimumab and nivolumab to determine appropriate label changes to the product safety information to include the potential risk of hemophagocytic lymphohistiocytosis (HLH).

HLH is a condition where large numbers of immune cells destroy other blood cells.

Ipilimumab and nivolumab are indicated to treat different types of cancers, including cancers of the skin, kidney, lung and liver.

Health Canada conducted a safety review of the risk of HLH associated with the use of ipilimumab or nivolumab following reports of HLH published in medical literature.

Health Canada has received one Canadian report of a cancer patient who developed HLH after treatment with nivolumab in combination with ipilimumab. The report was considered serious and resulted in death. Additionally, Health Canada reviewed 21 international reports of HLH following treatment with nivolumab and ipilimumab, either used alone or in combination. All reports were considered serious, and six of 21 cases were fatal. However, Health Canada could not confirm a causal relationship between the medicines and death in these cases. The medical literature suggests a potential link between the use of the medicines and the development of HLH.

Reference:

Summary Safety Review, Health Canada, 24 June 2019
(www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletter No.2, 2019: Risk of serious blood disorder in Japan)

Non-steroidal anti-inflammatory drugs (NSAIDs)

Risk of cardiovascular adverse events

New Zealand. Medsafe has announced that all non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of a cardiovascular adverse event.

NSAIDs reduce inflammation by inhibiting the production of cyclo-oxygenase (COX)-1 and 2, and are generally indicated to reduce pain, decrease fever and decrease inflammation.

Since the Medicines Adverse Reactions Committee (MARC) previously discussed the cardiovascular safety of diclofenac and ibuprofen, several new studies on the cardiovascular safety of NSAIDs have been published.

The MARC reviewed the cardiovascular safety of NSAIDs including two clinical trials and two meta-analyses. MARC concluded that it is currently not possible to differentiate or rank NSAIDs by their individual cardiovascular risk profiles.

NSAIDs should be avoided in patients with established cardiovascular disease, and patients should be informed of the risk of NSAIDs. If required, NSAIDs should be used at the lowest effective dose for the shortest duration possible.

Reference:

Prescriber Update, Vol. 40, No.2, Medsafe, June 2019
(www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.4, 2015: Small increased cardiovascular risk with daily doses at or above 2,400mg in Ireland)

Proton pump inhibitors (PPIs)

Risk of rebound acid hypersecretion (RAHS)

New Zealand. Medsafe has announced that rebound acid hypersecretion (RAHS) has been reported in patients after stopping prolonged treatment with proton pump inhibitors (PPIs).

PPIs (omeprazole, lansoprazole and pantoprazole) inhibit gastric acid secretion and have several indications such as the short-term treatment of benign duodenal and gastric ulcers and the eradication of *Helicobacter pylori* in combination with antibacterials.

RAHS is the recurrence of symptoms due to an increase in gastric acid secretion above pretreatment levels after stopping PPI therapy. Symptoms of RAHS may include heartburn, regurgitation or dyspepsia.

For many people, short-term PPI use (4-8 weeks) is appropriate. A step-down

approach should be considered when stopping PPI therapy. Stepping down involves gradually reducing the dose over time before stopping the medicine completely. Alternative treatments such as histamine H2-receptor antagonists or antacids may be useful to manage rebound symptoms.

Reference:

Prescriber Update, Vo. 40, No.2, Medsafe, June 2019 (www.medsafe.govt.nz/)

Rivaroxaban and other direct-acting oral anticoagulants (DOACs)

Increased risk of recurrent thrombotic events

United Kingdom. The MHRA has announced that a clinical trial has shown that there is an increased risk of recurrent thrombotic events associated with rivaroxaban (Xarelto®) use compared to warfarin, in patients with antiphospholipid syndrome and a history of thrombosis.

Direct-acting oral anticoagulants (DOACs) are indicated for the treatment and prevention of venous thromboembolism, and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more risk factors. DOACs available are rivaroxaban, apixaban (Eliquis®), edoxaban (Lixiana®) and dabigatran (Pradaxa®).

A clinical trial compared rivaroxaban to warfarin in 120 patients and showed that use of rivaroxaban in patients with antiphospholipid syndrome could be associated with increased rates of recurrent thrombotic events compared to therapy with warfarin.

There have been no completed clinical trials for use of other

DOACs such as apixaban, edoxaban and dabigatran in patients with antiphospholipid syndrome, therefore available data for these medicines are limited. However, available data suggest that other DOACs may also be associated with a similarly increased risk of recurrent thrombotic events as with use of rivaroxaban.

Health-care professionals are advised to review whether continued treatment with a DOAC is appropriate for patients diagnosed with antiphospholipid syndrome and consider switching to a vitamin K antagonist such as warfarin.

Reference:

Drug Safety Update, MHRA, 19 June 2019 (www.gov.uk/mhra)

Tocilizumab

Risk of hepatotoxicity

1. Australia. The Therapeutic Goods Administration (TGA) has announced that serious drug-induced liver injuries, including acute liver failure, hepatitis and jaundice, have been observed with the administration of tocilizumab (Actemra®).

Indications of tocilizumab include treatment of rheumatoid arthritis, giant cell arteritis in adults, and polyarticular juvenile idiopathic arthritis in patients of two years of age and older. Tocilizumab is known to cause transient or intermittent mild to moderate elevation of hepatic transaminases.

The TGA advises patients treated with tocilizumab to be closely monitored for liver adverse events and advised to seek immediate medical advice if they have signs or symptoms of hepatotoxicity such as jaundice, dark urine, itch, loss of appetite, nausea or vomiting.

The current Product Information does not recommend treatment in patients with elevated alanine

aminotransferase (ALT) or aspartate aminotransferase (AST). The TGA is reviewing the data on hepatotoxicity with tocilizumab and may recommend changes to the Product Information.

Reference:

Medicines Safety Update, TGA, 11 July 2019 (www.tga.gov.au)

2. United Kingdom. The MHRA has announced that serious liver injury has been reported in patients treated with tocilizumab (RoActemra®), with an onset ranging from two weeks to more than five years after initiation. Liver injury includes acute liver failure and hepatitis, and some cases required liver transplantation.

A recent EU cumulative review found that treatment was associated with severe liver injury. The review of data from clinical trials, non-interventional studies, spontaneous reports, and the published literature identified eight cases of tocilizumab-related drug-induced liver injury worldwide.

ALT and AST levels should be measured before starting treatment with tocilizumab and monitored every four to eight weeks for the first six months of treatment followed by every 12 weeks thereafter.

Reference:

Drug Safety Update, MHRA, 17 July 2019 (www.gov.uk/mhra)

Zopiclone

Risk of central nervous system adverse events

New Zealand. Medsafe has announced that the higher dose (7.5 mg) of zopiclone (Imovane®) is likely to cause central nervous system adverse events in the elderly.

Zopiclone is indicated for short-term treatment of insomnia. The approved adult dose is 7.5 mg,

up to a maximum of four weeks. The recommended dose for elderly patients is 3.75 mg.

In elderly, the elimination half-life of zopiclone is prolonged to approximately seven hours, compared with five hours in younger adults. The risk of next-day hangover effects such as drowsiness, cognitive impairment and dizziness is, therefore higher in the elderly. Also, psychiatric adverse events, including depression, suicidality, psychosis and schizophrenia have been associated with the use of zopiclone, and are more likely to occur in the elderly.

Reference:

Prescriber Update, Vo. 40,
No.2, Medsafe, June 2019
(www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter
No.6, 2014: Risk of next-day impairment in
Canada)

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 20 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC's current routine signal detection process. International pharmaceutical companies, when identified as uniquely responsible for the drug concerned, are invited to comment on the signal text. Signals are thereafter communicated to National Pharmacovigilance Centres, before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version. More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 26). For information on the UMC Measures of Disproportionate reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. For more information, on the UMC Measures of Disproportionate Reporting etc., visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: signals@who-umc.org.

Combination products containing guaifenesin, paracetamol, and phenylephrine reported with severe upper abdominal pain

Dr. Kristina Star, Uppsala Monitoring Centre and Annet van Erp-van Boekel, the Netherlands Pharmacovigilance centre Lareb

Summary

In April 2018, a signal detection screening in VigiBase, the WHO global database of individual case safety reports, was designed to detect safety concerns reported by patients. A case series with upper abdominal pain following intake of combination products containing guaifenesin, paracetamol, and phenylephrine was highlighted as meriting further assessment. The in-depth review of the 29 cases in VigiBase, encompassing all reports with gastrointestinal (GI) related pain, revealed a pattern where patients described severe upper abdominal pain following the intake of these products, frequently with a sudden onset and recovery after stopping the drug. The patient information leaflets (PIL) for these combination products describe abdominal/stomach discomfort or stomach aches/upsets. However, in some of the PILs, the only GI-related adverse reactions listed are nausea and vomiting. Patients might not recognise the descriptions in the PIL as a reflection of their experiences of severe abdominal pain (one patient almost called the ambulance), so consideration should be made to better describe abdominal pain in the information to patients.

Introduction

Combination products containing guaifenesin, paracetamol, and phenylephrine are approved for

symptoms associated with colds, flu, headaches, blocked nose, sore throat, chills, fever, and chesty coughs.¹ These products are marketed worldwide and are mostly sold over-the-counter.²

There are several brands on the market with various dosage strengths and formulations, e.g., liquid, tablet, capsule and powder for oral solutions. In the United Kingdom (UK), the strengths are either 100 or 200 mg for guaifenesin; 250, 500, 1000 mg for paracetamol; and 5, 6.1, 10, 12.2 mg for phenylephrine hydrochloride.¹ In the United States (US), there is a range of products with other formulations and strengths.³ Products are approved from the age of 12, or of 16 in the UK¹, and from six years of age in the US.³

The MedDRA (Medical Dictionary for Regulatory Activities) preferred terms (PT) 'abdominal pain' and 'abdominal pain upper' include long lists of lowest level terms, such as stomach ache, stomach cramps or stomach pain but these terms in themselves do not cover the severity of the adverse reaction.

Reports in VigiBase

In April 2018, a signal detection screening in VigiBase, the WHO global database of individual case safety reports, was designed to detect safety concerns reported by patients. A case series with

upper abdominal pain following the intake of combination products with guaifenesin, paracetamol, and phenylephrine was highlighted as meriting in-depth assessment as the patient descriptions of the event differed from that in the product information.

In October 2018, VigiBase contained 197 reports with combination products containing guaifenesin, paracetamol, and phenylephrine, of which gastrointestinal (GI) disorders were the most frequently reported MedDRA system organ class, with 'abdominal pain upper' (22 reports), vomiting (16) and nausea (15) listed as the most frequently reported PTs. When searching the MedDRA high level term 'gastrointestinal and abdominal pains (excl. oral and throat)' with the combination product, 29 unique reports were retrieved after exclusion of one duplicate report. Summary characteristics are given in Table 1.

The patients in this case series described experiences of severe and often sudden abdominal pain in temporal association of starting combination products with guaifenesin, paracetamol, and phenylephrine. In all but one report, the combination product was recorded as the single suspect drug. Patients described their upper abdominal pain with or without nausea, vomiting, diarrhea, malaise and dizziness. Additional co-reported symptoms were general discomfort, other pains or GI symptoms. Co-reported events concerned mere symptoms, except for one case, co-reported with the diagnosis legionella pneumonia, which referred to a published literature case. One 71-year-old male patient reported gastrointestinal polyp haemorrhage together with upper abdominal pain. Concomitant drugs for this patient were tamsulosin, atenolol, and gabapentin. Further details for this case were not registered in VigiBase.

Chronic concomitant use of medicines was recorded with the combination product for nine patients, such as levothyroxine, citalopram, fluticasone and the combination product estradiol and norethisterone. Eight patients were recorded with paracetamol concomitantly. One young adult was co-reported with two paracetamol products but information on timing and dosages for paracetamol were missing from these reports.

The dosage forms of the suspected combination products for the VigiBase reports were, where it could be determined, liquids (12), tablets (1), capsules (7), and powder for oral solution (1). Dosage strengths recorded in these reports were within normal ranges for adults.

Patients' descriptions of abdominal pains

The following are some of the free text descriptions

from the patients:

- *"Sharp/cramping pains in stomach. Right in between the ribs. Centre of stomach Nearly phoned ambulance. Pain was unbearable at one point."*
- *"Sudden severe stomach cramps, dizziness, raised temperature and sudden severe vomiting"*
- *"...experienced severe stomach pain with 10 minutes [sic] of taking the tablets I then felt sick and vomited twice. I then felt ok apart from my cold symptoms."*
- *"...experienced extreme stomach pain and vomiting just minutes after the medicine was taken, lasted about 30 minutes before returning to normal."*
- *"Within seconds of taking experienced severe pain in the stomach causing collapse and projectile vomiting. ...the pain was so extreme ... collapse to the floor in pain."*
- *"Severe abdominal pain, abdominal cramps and diarrhoea."*

Disproportionality analysis for the combination product and single substances

Based on the overall reporting of the MedDRA PT 'abdominal pain upper' for combination products containing guaifenesin, paracetamol, and phenylephrine, IC analysis found the association to be disproportionally reported.^{4,5} Table 2 displays the statistics for PTs 'abdominal pain upper' with the combination product and the single substances.

'Abdominal pain upper' for the combination product and the single substances was, except for phenylephrine, disproportionally reported in VigiBase.

Literature and Labelling

The Summary of Product Characteristics (SmPC) for combination products with guaifenesin, paracetamol, and phenylephrine in the UK list abdominal discomfort, nausea and vomiting in relation to guaifenesin; nausea, vomiting and diarrhoea in relation to phenylephrine; and pallor, nausea, vomiting, anorexia and abdominal pain in the overdose section for paracetamol.¹

In some of the Patient Information Leaflets (PILs), the only gastrointestinal related adverse reactions listed are nausea and vomiting, and where abdominal discomfort is mentioned, it is expressed as abdominal/stomach discomfort or stomach aches/upsets.¹

Combination products with these substances in the US list upset stomach or stomach pain as signs of liver problems.⁶

Table 1. Summary characteristics of 29 VigiBase reports with combination products containing guaifenesin, paracetamol, and phenylephrine and the MedDRA high level term 'gastrointestinal and abdominal pains (excl. oral and throat)', October 2018.

Characteristic	Case series under assessment
Age (median / range)	41 years / 18-71 years
Patient sex distribution	23 females / 6 males
Geographical spread	Czech Republic, Hungary, Italy, Latvia, Portugal and Romania (n=1 each), United Kingdom (n=21), United States of America (n=2)
Reporter types	26 consumers; 2 other health professionals; 1 pharmacist
Single suspect drug	28 reports*
Single reported drug	11 reports
Time-to-onset	17 reports same day, 6 reports after 1 day, 1 report after 2 days
Withdrawal/Recovered	18 reports with drug withdrawn and reaction abated 4 reports with drug withdrawn but no effect observed

*The 29th report listed 'Covonia dry and tickly cough' containing glycerol as a co-suspected drug.

Table 2. Combination and single substances with guaifenesin, paracetamol, and phenylephrine reported with MedDRA preferred term abdominal pain upper in VigiBase*

Suspected substance	Number of reports for substance	Number of reports with abdominal pain upper	Calculated expected number of reports	IC	IC ₀₂₅	Number of countries***
Guaifenesin; Paracetamol; Phenylephrine	197	22	1.5	3.51	2.84	6
Guaifenesin	5 218	97**	39	1.30	1.00	2
Paracetamol	119 001	1 208**	892	0.44	0.35	41
Phenylephrine	1 914	7**	14	-0.99	-2.25	3

*VigiBase data up to 28 October 2018.

**Individual case assessment was not done for single substances, so alternative explanations for the abdominal pain in these reports could exist.

***Number of countries from which reports were sent

Discussion

It is uncertain which of the substances in the combination product most likely caused the sudden abdominal pain. Guaifenesin has been described as inducing gastrointestinal discomfort, nausea and vomiting,² and these reactions are listed in connection to guaifenesin in the SmPCs for these combination products.¹ It is unclear why guaifenesin would induce sudden gastric pain in some individuals, but it does not seem unreasonable because of its stimulation of mucosa receptors in the gastrointestinal tract.⁷ Paracetamol overdose can cause abdominal pain as a first sign of liver damage, but in none of the 29 VigiBase cases was an over dosage suggested, however, eight patients used paracetamol concomitantly with the combination product. None of these cases included information on dosages for these co-reported products, so a possibility of overdose cannot be excluded. Phenylephrine hydrochloride acts with alpha-1 receptor stimulation, resulting in vasoconstriction in vessels of the skin, abdominal viscera and kidney, and theoretically abdominal pain could result from a decreased blood flow to the gastrointestinal tract.⁸ Only a few reports of

abdominal pain have been received in VigiBase for phenylephrine as a single substance. One case in the literature describes a 70-year-old woman with phenylephrine-associated ischaemic colitis presenting with nausea, vomiting, abdominal pain, diarrhoea, and acute onset of haematochezia following 'a lot' of aspirin and phenylephrine use for sinusitis and nasal congestion.⁹ This case is interesting in the light of the 71-year-old male in the VigiBase case series, who experienced gastrointestinal polyp haemorrhage together with upper abdominal pain following use of the combination product. Further investigation of more serious consequences of phenylephrine use may be warranted.

In a study investigating the bioavailability of a new oral syrup product containing guaifenesin, paracetamol, and phenylephrine, 45 patients were enrolled. Two patients reported GI adverse events (nothing more was specified) following the use of the test product consisting of the new oral syrup, and four patients reported GI adverse events following the use of the reference product consisting of an established oral liquid containing the same combination of substances. The authors considered

the reported GI adverse events in this study as related to the liquid formulation, without any further discussion.¹⁰ In the VigiBase case series, the drug formulations used by the patients were liquid, tablet, capsule, and powder for oral solution, but patients in this case series still experienced sudden, severe abdominal pain in temporal association with these products.

There is a possibility that some of the excipients in the products used by the patients in the VigiBase case series would cause abdominal pain. Sorbitol has been reported to be associated with abdominal pain, bloating and diarrhoea¹¹, and was listed as the cause for abdominal pain in the label for one of the Swedish guaifenesin products.¹² However, the products used by the patients in the VigiBase series did not always include sorbitol, so this excipient would not be the contender in many of the cases included in this signal.

An obvious confounding factor is the underlying disease in these cases, where abdominal pain, nausea and vomiting could occur. However, for many cases, the upper abdominal pain had a sudden onset after drug intake, and there was recovery reported after stopping the drug, suggesting a causal relationship to the combination product.

Conclusion

The VigiBase reports revealed a pattern where patients described severe upper abdominal pain following the intake of combination products containing guaifenesin, paracetamol, and phenylephrine, many times with a sudden onset and recovery after stopping the drug. The PILs for these products describe abdominal/stomach discomfort or stomach aches/upsets, however in some PILs, the only GI-related adverse reactions listed are nausea and vomiting. Patients might not recognise the descriptions in the PILs as a reflection of their severe experiences of abdominal pain, so consideration should be made to better describe abdominal pains in the information to patients.

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Methylphenidate and lockjaw

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Summary

Methylphenidate and trismus (lockjaw) was identified as a potential signal in a screening of VigiBase, the WHO global database of individual case safety reports, focusing on patient reports. The association is disproportionately over-reported compared to the overall rate in VigiBase with 27 observed cases, compared to the expected 8.3 (review of VigiBase on 2 May 2018). All cases which reported any of the terms "trismus", "jaw stiffness", "jaw joint rigid state of", "tightness in jaw" or "tightness of jaw muscles", were included in this assessment. In total, 38 reports were analysed. Overall, the cases support an association between methylphenidate and trismus, with the majority reporting methylphenidate as the only suspect drug and with eight cases reporting a positive dechallenge, of which one also reported a positive rechallenge. In addition, the dopamine-altering effect of methylphenidate provides a plausible mechanism behind trismus, which in these cases was thought to be a dystonic reaction. Trismus or lockjaw is not labelled for methylphenidate in either the Summary of Product Characteristics or the Patient Information Leaflet. However, the similar terms muscle tightness, muscle spasms, muscle twitching and muscle cramps are described. Nonetheless, for patients, it might not be obvious enough from these terms that jaw-related reactions might occur, and therefore they could benefit from more clarity as that might assist them in deciding to start or continue their treatment.

Introduction

In April 2018, during a screening of VigiBase, the WHO global database of individual case safety reports, focusing on patient reports, the combination of methylphenidate and muscle tightness was identified as needing further in-depth assessment. Several cases described jaw tightness, and further exploration of VigiBase revealed many cases of trismus (lockjaw).

Methylphenidate is a centrally acting sympathomimetic indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD).¹ The US Food and Drug Administration (FDA) first approved methylphenidate back in 1955, for various psychological disorders, and in the 1970s it was introduced to treat ADHD.² Even though the drug has been on the market for a long time, the mechanism by which it exerts its therapeutic effect is still not clearly established. It is thought to facilitate the action of dopamine and norepinephrine through three mechanisms: 1) inhibition of reuptake, 2) facilitation of release into the synaptic cleft, and, 3) inhibition of the catabolic activity of monoamine oxidase.³

Trismus, or lockjaw, is the inability to open the mouth, usually because of muscle spasms. Causes include physical trauma, oral/dental surgery, infections, and temporomandibular joint disease (e.g. rheumatoid arthritis). Trismus can also be part of a drug-induced dystonic reaction. Antipsychotics (e.g. risperidone, aripiprazole) and antiemetics (e.g. metoclopramide) are known to cause dystonia, and it seems to be caused by an abnormal dopaminergic activity involving the basal ganglia.⁴

Dystonia is characterized by "muscular contractions or spasms that result in abnormal fixed postures or positions of the jaw, neck, shoulders, trunk, and extremities".⁵ It can also result in twisting and repetitive movements. The symptoms are associated with pain and distress, and can cause difficulty with walking, speech, head turning, and swallowing. Dyskinesia, on the other hand is characterized by abnormal, involuntary, repetitive and persistent movements affecting the mouth and face, extremities and the trunk.⁶ Tardive dyskinesia can develop after treatment with dopamine receptor-blocking agents, usually one month after starting treatment.⁵ Symptoms are not painful but can still be debilitating.

Trismus, or any other jaw-related event, is not labelled for methylphenidate, but muscle tightness, muscle spasms, muscle twitching and muscle cramps are described.^{1,7} The labelled events are general and may not be specific enough for the patient to be able to connect them to trismus. Hence, the possible association of methylphenidate and trismus was investigated further.

Reports in VigiBase

The association of methylphenidate and trismus is disproportionately over-reported compared to the overall reporting rate in VigiBase (IC₀₂₅: 1.04). A total of 27 cases was observed, compared to the expected 8.3 (2 May 2018).

Cases which reported the MedDRA preferred term (PT) "trismus" or any of the lowest level terms (LLTs) "jaw joint rigid state of", "jaw stiffness", "tightness in jaw" or "tightness of jaw muscles", were included in the assessment (see table 2 for which search terms were applied, displayed in the context of the MedDRA hierarchy).

The 44 cases retrieved from VigiBase had been entered between 1 November 2000 and 2 May 2018. Six suspected duplicate reports were excluded leaving 38 cases for analysis, of which 29 had been coded with trismus. The characteristics of the case series are summarized in Table 1. For more details on the individual cases, please refer to Table 3. Cases which reported oromandibular dystonia (PT) were reviewed, but since they

concerned events quite different from trismus such as lingual dystonia (affecting the tongue), they were not included in our analysis.

Methylphenidate was the only suspected drug in 27 cases (of which three cases reported other concomitant drugs). The drug was withdrawn in 14 cases, the dose was reduced in one, the dose was

increased in one, the dose was not changed in five, and the action taken with the drug was unknown in 13 cases. For the four remaining cases, trismus occurred upon withdrawal or dose reduction of methylphenidate (the cases are described further down).

Table 1. Characteristics of the case series for trismus (PT), jaw joint rigid state of, jaw stiffness, tightness in jaw and tightness of jaw muscles (all LLTs) in association with methylphenidate.

Number of reports	38
Reporting countries	USA (14), Netherlands (14), Canada (3), Denmark (1), France (2), Iceland (1), New Zealand (1), Norway (1), South Africa (1)
Sex	17 females, 20 males, 1 unknown
Age	Range: 5 – 60 years Median: 21 years Mean: 25 years Age was unknown in one case
Time-to-onset (TTO)	Range: 30 minutes – 1 year TTO reported in 22 cases. TTO was within one day in ten of these cases. In four cases trismus occurred after abrupt withdrawal (3) or dose reduction (1) of methylphenidate

Upon dechallenge or dose reduction, the reaction abated in eight cases, no effect was observed in four cases and in three cases the outcome was unknown. In seven of the eight cases of positive dechallenge, methylphenidate was the only suspect drug, with no other concomitants reported. In one case (20), a positive rechallenge was reported. The case describes a 40-year-old female who experienced extrapyramidal symptoms consisting of involuntary movement of the tongue and trismus 30 minutes after methylphenidate administration. The drug was withdrawn, and the patient recovered. The patient was then treated with methylphenidate slow-release and the symptoms were reported to be less severe. The case was first described in a signal published by the Netherlands Pharmacovigilance Centre Lareb.⁸

In three cases, trismus resolved spontaneously without changing the methylphenidate treatment. One case (3) concerned a 29-year-old female who experienced one episode of trismus after increasing the methylphenidate dose from 30 to 40 mg. The adverse event resolved spontaneously, and the patient did not experience similar events later. No other concomitant drugs were reported. In another case (22), a 21-year-old female experienced trismus two days after administration of methylphenidate. The patient was reported to be recovering without changing the drug treatment. She also used oestrogen with levonorgestrel (treatment with propranolol was also reported which started after trismus occurred). The third case (38) describes a 35-year-old female experiencing tightness of jaw muscles within a month after starting methylphenidate treatment

which she recovered from without changing the administration of methylphenidate.

Table 2. MedDRA terms in bold were used for retrieval of cases with jaw-related events

MedDRA preferred term	MedDRA lowest level term
Trismus	Jaw cramp Jaw movements disturbance Jaw spasm Locked jaw Rigidity masticatory Spasm temporomandibular Trismus
Joint stiffness	Ankle stiffness Arthrosclerosis Early morning joint stiffness Jaw joint rigid state of Jaw stiffness Joint stiffness Joint tightness Stiff joint Stiff knees Stiffness hip Stiffness joints
Muscle tightness	Muscle tension Muscle tightness Neck tightness Periorial tension Tightness in jaw Tightness of back muscles Tightness of jaw muscles

Concomitant treatment with antipsychotics (aripiprazole, risperidone and/or ziprasidone) was reported in five cases and were reported as suspected in four of the cases. Antipsychotics are known to cause dystonia, although trismus is not specifically labelled as an adverse reaction except for ziprasidone.⁹ In three of these cases (2, 12, 23), onset of trismus followed abrupt discontinuation of methylphenidate whilst on concomitant treatment with antipsychotic drugs. In case 12, diphenhydramine was also withdrawn.

In another case (24) the patient was not treated with antipsychotics but still experienced trismus after a rapid decrease in the methylphenidate dose. The patient had used methylphenidate for one year and was normally treated with 80-120 mg/day. On the same day as she took only 20 mg, she developed trismus and jaw pain. The patient was also taking metoprolol and sumatriptan for migraine, both reported as suspected.

Literature and Labelling

Trismus (or any other jaw-related adverse reaction) is not described in the UK Summary of Product Characteristics (SmPC) or in the US FDA label for methylphenidate.^{1,7} However, muscle tightness, muscle spasms, muscle twitching and muscle cramps are all described although they don't refer specifically to the jaw or mouth.

In the UK Patient Information Leaflet (PIL), the following adverse reactions are described: "muscle spasms which you cannot control affecting your eyes, head, neck, body and nervous system", "muscle tightness, muscle cramps", "muscle pain, muscle twitching".¹⁰

Jaw-specific reactions are not covered in the leaflet, although "uncontrolled speech and body movements" and "clenching or grinding your teeth" are.

In 2012, the Netherlands Pharmacovigilance Centre Lareb published a signal describing the association between trismus and the use of methylphenidate and dexamphetamine.⁸ At the time of the assessment, their database contained seven cases of jaw cramp/trismus associated with methylphenidate use (all of which are included in this assessment) and two cases of trismus associated with dexamphetamine use. Trismus and methylphenidate was disproportionately reported in the Lareb database, in the WHO global database and in the Eudravigilance database. In 2013, Prescrire wrote about methylphenidate and trismus, referring to Lareb's signal, and argued that trismus should be recognised as an adverse reaction in patients exposed to methylphenidate.¹¹

There are several published case reports of methylphenidate-associated dystonic reactions in connection to concomitant use of antipsychotic drugs, including cases of dystonia occurring after abrupt methylphenidate withdrawal.¹²⁻¹⁵ In our case

series only five cases have concomitant antipsychotic medications, of which two are literature reports.^{12,13}

However, there are few literature cases of dystonia associated with methylphenidate-only treatment. Tekin et al describe a 15-year-old female who experienced involuntary extensor muscular contraction of her right hand and wrist together with tension and severe pain, nine days after taking 27 mg of modified-release methylphenidate.¹⁶ She was diagnosed with acute focal dystonic reaction which subsided after diazepam administration. A few years prior, the patient had experienced muscular contraction in her foot when she took immediate-release methylphenidate, which disappeared when the drug was stopped. In another case, a 7-year-old female diagnosed with ADHD was prescribed 5 mg of immediate-release methylphenidate twice daily.¹⁷ After her third dose, she developed dystonic movements characterized by turning the neck sideways and twisted facial muscles.

Discussion

The mechanism behind trismus reported in the cases was thought to be a dystonic reaction induced by the dopamine-altering mechanism of methylphenidate. A VigiBase search on 13 August 2018 revealed that there were 213 reports of methylphenidate and dystonias (MedDRA High Level Term, HLT). Among these, only 74 cases reported concomitant treatment with antipsychotics (aripiprazole, olanzapine, quetiapine, risperidone and/or ziprasidone) which are known to cause dystonia. We restricted the in-depth assessment to cases with reports of jaw-related events because we thought patients would benefit from knowing about these specific reactions as these can be distressing and painful. The product information does not describe dystonia as an adverse reaction, but it could be argued its symptoms are covered by the mention of muscle tightness, spasms, and cramps, while lacking a description of specific body parts affected.

The mechanism behind dystonia is unclear but it seems to be caused by an abnormal dopaminergic activity involving the basal ganglia. Two contrasting hypotheses have been proposed: 1) dopaminergic hypofunction within basal ganglia leading to overactivity of the cholinergic system, and 2) hyperactivity of dopaminergic pathways.⁵ Therefore, any drug that alters dopamine signalling, whether by inhibiting it (such as for antipsychotics), or by increasing it, could in theory cause dystonic reactions. So, it could be hypothesized that methylphenidate can cause dystonic reactions such as trismus, through its stimulatory effect on dopamine signalling (inhibits reuptake and facilitates release of monoamines into synaptic cleft).

For six cases there was some doubt about whether the patients experienced the reported trismus or if

they experienced dyskinetic reactions. Dyskinesia is labelled for methylphenidate. The narrative in these cases described reactions such as "jaw moving back and forth", "constantly drops jaw and mouth", "jaw twitching", "jaw movements" and "motorial agitation" reflecting a possible coding issue.

Three patients in this assessment recovered from trismus without changing the methylphenidate treatment. These observations might somewhat weaken the hypothesis that methylphenidate may induce trismus.

However, the literature reports of dystonia associated with methylphenidate withdrawal¹²⁻¹⁵ suggest that methylphenidate could cause dystonic reactions by disrupting the dopamine balance. In these cases, the patients were treated with both methylphenidate which stimulates dopamine action, and with antipsychotics which block dopamine action and seemed to have reached a balance in dopamine levels. They only experienced dystonic reactions when methylphenidate was withdrawn, that is when the dopamine balance was disrupted.

Having trismus can be painful and distressing for the patient. For example, in one case the patient could not sleep because of it. In another case, the patient was unable to move his jaw or close his mouth. He was taken to the emergency room and prescribed diphenhydramine to treat it, but his jaw would still lock up. Therefore, being able to connect that trismus could be an adverse effect of methylphenidate could play a role in deciding whether to start or continue with the treatment, especially if it is a recurring problem.

Conclusion

In conclusion, there is a signal for methylphenidate and trismus. Overall, the VigiBase cases presented here support this hypothesis, since:

- the majority of cases (70%) report methylphenidate as the only suspect drug.
- eight cases report a positive dechallenge, of which one reported a positive rechallenge.
- there was a plausible dopamine-altering pharmacological mechanism.
- trismus is plausible when considering other, more general, labelled events for methylphenidate such as muscle tightness, muscle spasms, and muscle cramps.
- over-reporting of the association compared with the overall reporting in VigiBase.

Trismus or lockjaw is not labelled for methylphenidate in either the SmPC or the PIL. Similar reactions are described in the label, but they do not specifically refer to the jaw. Patients may not therefore recognize trismus or other jaw-related reactions as an adverse drug reaction and could benefit from clearer labels. It is important that the

patient has all the necessary information which might affect their decision to start or continue a specific treatment. Since trismus is likely to be a dystonic reaction and dystonia is not specifically included in the label for methylphenidate, dystonia, as a possible adverse reaction to methylphenidate, should undergo in-depth case-assessment.

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Table 3. Characteristics of case reports in VigiBase of trismus in association with methylphenidate

Case number	Age/ Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Time-to-onset	Action taken with drug (dechallenge/rechallenge)	Outcome
1	5/M	Methylphenidate (S)	Eye disorder, Trismus, Vision blurred	Within 1 month after starting treatment but within 1 day after dose increase (from 18 to 27 mg)	Dose increased/No effect observed It is unclear if the dose increase refers to the increase from 18 to 27 mg which occurred before reaction onset.	Not recovered
2	11/M	Aripiprazole, Methylphenidate, Propofol (all S) Clonidine, Fentanyl, Rocuronium, Sevoflurane (all C)	Jaw disorder, Oromandibular dystonia, Trismus	-	- Comment: reaction occurred upon abrupt withdrawal of methylphenidate while still on concomitant treatment with antipsychotics The authors of this literature report suspect chronic aripiprazole and methylphenidate usage combined with propofol administration in the short-term absence of methylphenidate made this patient susceptible to dystonic reactions.	Recovered
3	29/F	Methylphenidate (S)	Decreased appetite, Dry mouth, Trismus	-	Dose not changed/Reaction abated Comment: trismus occurred after methylphenidate dose was increased from 30 to 40 mg. The event then resolved spontaneously without changing the dose.	Recovered
4	-/F	Methylphenidate (S)	Depression, Drug effect incomplete, Irritability, Joint stiffness (LLT: Jaw stiffness), Musculoskeletal stiffness,	-	-	Unknown

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Case number	Age/ Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Time-to-onset	Action taken with drug (dechallenge/rechallenge)	Outcome
			Tension headache			
5	48/F	Methylphenidate (S)	Joint stiffness (LLT: Jaw stiffness), Mood altered	11.7 months	Drug withdrawn/Reaction abated	Recovered
6	42/F	Methylphenidate (S)	Alopecia, Hypoaesthesia, Hypoaesthesia oral, Muscle spasms, Trismus	2-3 days	Drug withdrawn/No effect observed	Not recovered
7	14/M	Methylphenidate (S)	Chest discomfort, Hypoaesthesia, Muscle tightness (LLT: Tightness in jaw), Tachycardia	-	-	-
8	40/F	Methylphenidate (S)	Finger deformity, Muscle tightness (LLT: Tightness of jaw muscles)	-	Drug withdrawn/-	Unknown
9	6/M	Methylphenidate (S)	Bruxism, Eating disorder, Tongue biting, Trismus	0 days Dose given in the morning before patient went to school and developed adverse reaction in the afternoon	Dose reduced/-	Unknown
10	60/M	Methylphenidate (S)	Feeling jittery, Mouth swelling, Muscle tightness (LLT: Tightness in jaw), Palpitations, Swollen tongue, Trismus	30 minutes	Drug withdrawn/Reaction abated	Recovered
11	8/F	Diphenhydramine, Methylphenidate (both S)	Dyspnoea, Insomnia, Trismus	4 hours	-/No effect observed	Not recovered
12	15/M	Diphenhydramine, Methylphenidate (both S) Bupropion, Ziprasidone (both C)	Pain, Swollen tongue, Tongue spasm, Trismus	-	- Comment: patient experienced the adverse reactions after withdrawal of both methylphenidate and diphenhydramine. Patient was treated with methylphenidate for 1.5 years before the withdrawal.	Recovered
13	5/M	Methylphenidate (S)	Dyskinesia, Eye disorder, Gait disturbance, Muscle twitching, Tongue disorder, Trismus	Within 1 day	Drug withdrawn/Reaction abated	Recovered
14	16/M	Methylphenidate, Oxybate sodium (both S) All other therapeutic products* (C)	Decreased appetite, Dizziness, Dystonia, Trismus, Weight decreased	-	-	-
15	42/M	Methylphenidate (S)	Anxiety, Cluster headache, Dizziness, Hyperhidrosis, Hypertension, Palpitations, Therapeutic response unexpected, Tremor, Trismus	Within 1 day	Dose not changed/Reaction abated Comment: the report narrative states that the methylphenidate dose was reduced from 108 to 90 mg after one year of treatment and withdrawn completely after four years. reports.	Recovered

Case number	Age/ Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Time-to-onset	Action taken with drug (dechallenge/rechallenge)	Outcome
					However, it is unclear whether the patient recovered from jaw cramps before or after the dose reduction/withdrawal.	
16	30/F	Methylphenidate, Omeprazole, Paroxetine (all I) Ethinylestradiol; Levonorgestrel (C)	Drug interaction, Hypertonia, Trismus	1 hour	Drug withdrawn/Reaction abated	Recovered
17	14/M	Methylphenidate (S)	Joint stiffness (LLT: Jaw stiffness), Peripheral coldness	“days”	Drug withdrawn/Reaction abated	Recovered
18	5/M	Amphetamine, Aripiprazole, Atomoxetine, Carbamazepine, Chlorpromazine, Clonidine, Dexamfetamine, Iloperidone, Lisdexamfetamine, Lithium, Methylphenidate, Quetiapine, Valproic acid, Ziprasidone (all S)	Aggression, Anxiety, Bruxism, Coordination abnormal, Crying, Decreased eye contact, Depressed mood, Drug ineffective, Dyskinesia, Fatigue, Homicidal ideation, Insomnia, Irritability, Mood altered, Oppositional defiant disorder, Poor quality sleep, Psychomotor hyperactivity, Sleep disorder, Speech disorder, Streptococcal infection, Suicidal ideation, Sydenham's chorea, Trismus	-	-	-
19	24/M	Methylphenidate (S)	Dyskinesia, Trismus	4 months	Drug withdrawn/No effect observed	Not recovered
20	40/F	Methylphenidate (S)	Extrapyramidal disorder, Trismus	30 minutes	Drug withdrawn/Reaction abated Rechallenge positive	Recovered
21	59/M	Methylphenidate (S)	Bruxism, Trismus	-	-	Unknown
22	21/F	Methylphenidate (S) Ethinylestradiol; Levonorgestrel, Propranolol (both C)	Trismus	2 days	Dose not changed/Reaction abated	Recovering
23	11/-	Aripiprazole, Methylphenidate (both S) Clonidine, Lithium (both C)	Affect lability, Aggression, Dystonia, Intentional self- injury, Joint stiffness (LLT: Joint stiffness), Muscle contracture, Trismus	-	- Comment: reaction occurred upon abrupt withdrawal of methylphenidate while still on concomitant treatment with antipsychotics. Patient had used the drug for four years but the reaction occurred 33 hours after the last dose.	Recovered
24	37/F	Methylphenidate, Metoprolol, Sumatriptan (S)	Pain in jaw, Trismus	1 year since starting treatment with methylphenidate but on same day as dose was reduced	- Comment: reaction occurred upon abrupt reduction of methylphenidate dose (from 80-120 mg to 20 mg). Patient had used the drug	Recovered

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Case number	Age/ Sex	Suspected (S), interacting (I) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Time-to-onset	Action taken with drug (dechallenge/rechallenge)	Outcome
					for one year and the reaction occurred on the same day as dose was reduced.	
25	41/F	Methylphenidate (S) Simvastatin (C)	Trismus	10 months	-/Reaction abated	Recovering
26	11/M	Cetirizine, Clonidine, Methylphenidate, Montelukast, Salbutamol (all S)	Hypersensitivity, Trismus	-	-	Not recovered
27	55/F	Methylphenidate (S) Duloxetine, Metformin (both C)	Joint stiffness (LLT: Jaw stiffness), Sleep disorder, Tourette's disorder	-	-	Not recovered
28	8/F	Methylphenidate (S)	Dysphagia, Logorrhoea, Restlessness, Trismus	8 h	Drug withdrawn/Reaction abated	Recovered
29	38/M	Methylphenidate (S)	Trismus	35 days	Dose not changed/No effect observed	Not recovered
30	8/M	Methylphenidate, Risperidone (both S)	Facial spasm, Pain in jaw, Somnolence, Tic, Trismus	-	Drug withdrawn/No effect observed	-
31	41/F	Methylphenidate (S)	Disturbance in attention, Joint stiffness (LLT: Jaw stiffness), Sleep disorder	-	-	Unknown
32	7/M	Methylphenidate (S)	Trismus	-	Drug withdrawn/No effect observed	Not recovered
33	18/M	Methylphenidate (S)	Blood pressure increased, Dizziness, Trismus	7 days	Drug withdrawn/-	Unknown
34	30/F	Amphetamine;Dexamfetam ine, Methylphenidate (both S)	Ear pain, Facial pain, Gingival disorder, Hyperacusis, Hypoaesthesia, Mastication disorder, Mobility decreased, Muscle spasms, Myalgia, Pain in jaw, Paraesthesia, Trismus	-	-	-
35	15/M	Methylphenidate (S)	Trismus	"years"	-	Unknown
36	8/M	Methylphenidate (S)	Crying, Neurological symptom, Torticollis, Trismus, Vision blurred	1 day	Drug withdrawn/Reaction abated	-
37	22/F	Methylphenidate (S)	Joint stiffness (LLT: Jaw stiffness), Hyperhidrosis, Tongue disorder	31 minutes	-	Not recovered
38	35/F	Methylphenidate (S)	Decreased appetite, Dry mouth, Headache, Muscle tightness (LLT: Tightness of jaw muscles), Sedation, Vertigo	Same month as starting treatment (exact unknown)	Dose not changed/Reaction abated	Recovered

*As reported, exact unknown

CAVEAT DOCUMENT

Statement of reservations, limitations and conditions relating to data released from VigiBase, the WHO global database of individual case safety reports (ICSRs).

Understanding and accepting the content of this document are formal conditions for the use of VigiBase data.

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

Tentative and variable nature of the data

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

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

Contingent influences: The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the adverse effects and other factors.

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

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

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

Prohibited use of VigiBase Data includes, but is not limited to:

- patient identification or patient targeting
- identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from VigiBase must include a statement:

- (i) recording 'VigiBase, the WHO global database of individual case safety reports (ICSRs)' as the source of the information
- (ii) explaining that the information comes from a variety of sources, and the probability that the suspected adverse effect is drug-related is not the same in all cases
- (iii) affirming that the information does not represent the opinion of the UMC or the World Health Organization.

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

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

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Update on Pharmacovigilance strengthening activities in Ethiopia

WHO has been working closely with the Ethiopian Food and Drug Administration (EFDA) to strengthen their pharmacovigilance system as part of the Smart Safety Surveillance project plan (see feature article in WHO Pharmaceuticals Newsletter, 2019, No2). Recent activities included: on-site discussions on improving reporting of adverse events (AEs) with health-care professionals at two health facilities in Addis Ababa; introduction of reporting tools; and organizing two pharmacovigilance strengthening workshops in Adama, Ethiopia.

On 3 July 2019 WHO delegates visited the Black Lion hospital, and St Petros Hospital, to gain an understanding of the current AE reporting situation, build awareness and introduce potential technological solutions to ease future reporting, manage data collection and prevent duplication of work. Tools such as the Med Safety app¹, and data management tool, Vigiflow were discussed. The test version of the med safety app is now available, and the launch campaign is planned for September 2019. Additionally, online reporting will be available towards the end of August 2019, and VigiFlow is now available at the seven regional pharmacovigilance sites. Health-care professionals at the two hospital sites expressed excitement over the new technological solutions and pharmacovigilance activities.

In August 2019, WHO organized two workshops: a basic pharmacovigilance training aimed for health-care professionals to build awareness in pharmacovigilance and promote AE reporting; and an advanced pharmacovigilance workshop on data management and analysis for pharmacovigilance regional centres and disease programmes in Ethiopia. The Medicines and Healthcare Products Regulatory Agency (MHRA) and the WHO Collaborating Centre for International Drug Monitoring, (Uppsala Monitoring Centre) collaborated with WHO in these workshops.

¹ The Med Safety app has previously been introduced in Burkina Faso, Zambia (see feature article in WHO Pharmaceuticals Newsletter, 2019 No3) and more recently in Ghana.