

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 also includes updates on Smart Safety Surveillance (3S) activities in India and Thailand.

Contents

Regulatory matters

Safety of medicines

Signal

Feature

© World Health Organization 2019

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

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

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

Suggested citation. WHO Pharmaceuticals Newsletter No.3, 2019: World Health Organization; 2019. Licence: CC BY-NC-SA 3.0 IGO.

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

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

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

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

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

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

Printed in Switzerland

Regulatory Matters

Clozapine	4
Denosumab	4
Direct-acting antivirals for chronic hepatitis C.....	4
Dulaglutide (genetical recombination)	4
Elvitegravir boosted with cobicistat	5
Fluoroquinolone antibiotics.....	5
Hydrochlorothiazide	5
Influenza HA vaccine.....	5
Irinotecan	6
Lenvatinib	6
Nivolumab (genetical recombination).....	6
Opioid pain medicines	6
Quetiapine.....	7
Sodium-glucose co-transporter 2 (SGLT2) inhibitors.....	7
Sorbitol, fructose (excipient).....	8
Vonoprazan	8

Safety of medicines

Alemtuzumab.....	9
Belimumab	9
Fluoroquinolone antibiotics.....	9
Insomnia medicines	9
Tofacitinib	10
Yellow fever vaccine.....	10

Signal

Desloratadine and the risk of experiencing dry eyes	11
Etanercept and ophthalmic herpes	13
Factor Xa inhibitors and haemospermia.....	15

Feature

Updates on Smart Safety Surveillance (3S) activities in India and Thailand.....	21
---	----

Clozapine

Risk of intestinal ulcer and intestinal perforation

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package insert for clozapine (Clozaril®) should be revised to include intestinal ulcer and intestinal perforation as adverse drug reactions.

Clozapine is indicated to treat resistant schizophrenia.

Four cases of intestinal perforation have been reported in Japan in patients treated with clozapine.

The MHLW and PMDA have concluded that revision of the package insert was 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, 19 March 2019 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.4, 2018: Gastrointestinal effects in Australia)

Denosumab

Risk of hypercalcaemia and multiple vertebral fractures

Japan. MHLW and PMDA have announced that the package insert for denosumab (Ranmark Subcutaneous Injection®) should be revised to include hypercalcaemia and multiple vertebral fractures following discontinuation of denosumab treatment, as adverse drug reactions.

Denosumab is indicated for bone lesions associated with multiple myeloma or bone metastasis of solid carcinoma and bone giant cell tumour.

Cases of hypercalcaemia after discontinuation of denosumab treatment have been reported overseas.

In a clinical study, there were cases of multiple vertebral fractures in the patient group taking denosumab compared to no cases in the placebo group.

One case involving hypercalcaemia after discontinuation of denosumab treatment has been reported in Japan during the previous three fiscal years. No cases involving multiple vertebral fractures after discontinuation of denosumab treatment have been reported.

Reference:

Revision of Precautions, MHLW/PMDA, 19 March 2019 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.4, 2018: Risk of multiple vertebral fractures in Japan; No.3, 2016: Contraindicated in patients with unhealed lesions from dental or oral surgery in Australia; No.4, 2015: Risk of Osteonecrosis of the jaw and hypocalcaemia in Egypt; No.5, 2014: Association with the risk of atypical femoral fractures in Canada; No.4, 2012: Risk of severe symptomatic hypocalcaemia, including fatal cases in Canada; No.4, 2012: Osteonecrosis of the Jaw (ONJ) in New Zealand)

Direct-acting antivirals for chronic hepatitis C

Risk of hypoglycaemia

Ireland. The Health Products Regulatory Authority (HPRA) is updating the Summary of Product Characteristics (SmPC) and Package Leaflets (PL) for direct-acting antivirals for chronic hepatitis C to include hypoglycaemia in patients with diabetes, particularly upon treatment initiation.

Direct-acting antivirals for chronic hepatitis C include daclatasvir (Daklinza®), sofosbuvir/velpatasvir (Epclusa®), and dasabuvir (Exviera®).

Rapid reduction in hepatitis C viral load during initial treatment with direct-acting antiviral therapy for hepatitis C may improve metabolism in patients with diabetes, and this could result in symptomatic hypoglycaemia.

Diabetic patients commencing treatment with direct-acting antivirals should be advised of the risk of hypoglycaemia in association with treatment. Also, patients with diabetes should be closely monitored for changes in blood glucose levels, particularly in the first three months of treatment.

Reference:

Drug Safety Newsletter, HPRA, April 2019 (www.hpra.ie)

(See WHO Pharmaceuticals Newsletter No.1, 2019: Risk of hypoglycaemia in patients with diabetes in UK)

Dulaglutide (genetical recombination)

Risk of severe diarrhoea and vomiting

Japan. MHLW and PMDA have announced that the package insert for dulaglutide (Trulicity Subcutaneous Injection®) should be revised to include severe diarrhoea and vomiting as adverse drug reactions.

Dulaglutide is indicated for treatment of type-2 diabetes mellitus.

A total of seven cases involving severe gastrointestinal disorders have been reported in Japan during the previous three fiscal years. Of the seven cases, a causal relationship to the product could not be excluded in three cases.

Reference:

Revision of Precautions, MHLW/PMDA, 19 March 2019 (www.pmda.go.jp/english/)

Elvitegravir boosted with cobicistat

Risk of treatment failure and maternal-to-child transmission of HIV-1

United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has announced that the product information for products containing elvitegravir boosted with cobicistat (Genvoya®, Stribild®) is being updated to warn against use during pregnancy.

Elvitegravir is an integrase inhibitor used to treat HIV-1. Cobicistat is a pharmacokinetic enhancer used to increase elvitegravir levels.

Pharmacokinetic data indicate that exposure of elvitegravir in preparations boosted with cobicistat, is lower during the second and third trimesters of pregnancy than during the postpartum period. Low elvitegravir exposure may be associated with an increased risk of treatment failure and an increased risk of HIV-1 transmission to the unborn child, and therefore elvitegravir and cobicistat combinations should not be used during pregnancy.

Reference:

Drug Safety Update, MHRA, 16 April 2019 (www.gov.uk/mhra)

Fluoroquinolone antibiotics

Risk of musculoskeletal and nervous systems damage

United Kingdom. The MHRA has announced that new restrictions for the indication of fluoroquinolones are being introduced to reduce the risk of disabling, long-lasting or potentially irreversible adverse reactions affecting the musculoskeletal and nervous systems.

Fluoroquinolone antibiotics available in the UK include: ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin. Fluoroquinolone antibiotics are indicated for serious, life-threatening bacterial infections.

The restrictions follow an EU wide safety review. Fluoroquinolones can very rarely cause long-lasting, disabling, and potentially irreversible adverse effects, sometimes affecting multiple systems, organ classes, and senses. The first signs of these adverse reactions include: tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy and central nervous system effects.

Health-care professionals should not prescribe fluoroquinolones for non-severe or self-limiting infections, or non-bacterial conditions. Health-care professionals should prescribe with special caution for people older than 60 years and for those with renal impairment or solid-organ transplants, because they are at a higher risk of tendon injury. Also, use of corticosteroids with a fluoroquinolone should be avoided, since co-administration could exacerbate fluoroquinolone-induced tendinitis and tendon rupture.

Reference:

Drug Safety Update, MHRA, 21 March 2019 (www.gov.uk/mhra)

(See WHO Pharmaceuticals Newsletter No.1, 2019: Risk of tendon damage and neuropathies in Ireland; No.6, 2018: Risk of long-lasting and disabling effects in Europe; No.2, 2017: Potential risk of persistent and disabling side effects in Canada; No.5, 2016: Disabling and potentially permanent adverse effects of the tendons, muscles, joints, nerves, and central nervous system in USA)

Hydrochlorothiazide

Risk of non-melanoma skin cancer

New Zealand. Medsafe has announced it is working with sponsors of hydrochlorothiazide-containing products to update the product information to include information about the risk of non-melanoma skin cancer.

Hydrochlorothiazide is used in combination with cilazapril, quinapril, losartan or amiloride, to treat high blood pressure and build-up of excess fluid in the body (oedema).

While the mechanism is unknown, hydrochlorothiazide has skin photosensitizing effects. Patients who are at higher risk of developing non-melanoma skin cancer (e.g. personal or family history of skin cancer) should take protective measures in any case. Also, health-care professionals should encourage patients taking a hydrochlorothiazide preparation to check their skin and lips regularly and report any changes or new skin lesions or moles.

Reference:

Safety Communications, Medsafe, 15 April 2019 (www.medsafe.govt.nz/)

(See WHO Pharmaceuticals Newsletter No.2, 2019: Potential risk of non-melanoma skin cancer (NMSC) in Canada and Singapore; No.1, 2019: Risk of non-melanoma skin cancer in Egypt; No.6, 2018: Risk of non-melanoma skin cancer in UK)

Influenza HA vaccine

Risk of acute generalised exanthematous pustulosis

Japan. MHLW and PMDA have announced that the package inserts for influenza HA vaccines (Influenza HA Vaccine KMB® and other preparations) should be revised to include acute generalised

exanthematous pustulosis as an adverse drug reaction.

Influenza HA vaccine is indicated for prophylaxis of influenza.

One case associated with acute generalised exanthematous pustulosis has been reported in Japan during the previous three fiscal years. A causal relationship with the product could not be excluded for this case.

Reference:

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

(See WHO Pharmaceuticals Newsletter No.6, 2018: Possible risk of lichen planus or lichenoid drug eruption in New Zealand)

Irinotecan

Risk of serious and fatal thromboembolic events

United Kingdom. The MHRA has updated the Summary of Product Characteristics (SPC) for irinotecan (Onivyde®) to include warnings of the risk of thromboembolic events.

Irinotecan is indicated to treat metastatic adenocarcinoma of the pancreas, in combination with 5-fluorouracil and leucovorin, in adults who have progressed following gemcitabine-based therapy.

A routine EU review assessed serious cases of thromboembolic events in patients receiving irinotecan. In the cumulative review from October 2015 to April 2018, 23 serious cases of thromboembolic events were identified, of which four were fatal. The reported events included pulmonary embolism, vena cava thrombosis, deep vein thrombosis, catheter site thrombosis and subclavian vein thrombosis.

The risk of thromboembolic events has been included in the product information for irinotecan since it was licensed, but due to the increased

reporting frequency and the seriousness of the reported events, additional warnings were added to the SPC, highlighting the need for a thorough medical history to identify patients with multiple risk factors.

Reference:

Drug Safety Update, MHRA, 21 March 2019 (www.gov.uk/mhra)

Lenvatinib

Risk of interstitial lung disease

Japan. MHLW and PMDA have announced that the package insert for lenvatinib (Lenvima®) will include interstitial lung disease as an adverse drug reaction.

Lenvatinib is indicated for unresectable thyroid cancer and unresectable hepatocellular carcinoma.

Eleven cases of interstitial lung disease have been reported in Japan during the previous three fiscal years. Of these cases, a causal relationship with the product could not be excluded in four cases. Also, a total of four patient mortalities have been reported, and of the four cases a causal relationship with the product could not be excluded for one.

Reference:

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

(See WHO Pharmaceuticals Newsletter No.6, 2018: Risk of pneumothorax in Japan)

Nivolumab (genetical recombination)

Risk of pituitary impairment

Japan. The MHLW and PMDA have announced that the package insert for nivolumab (Opdivo®) should be revised to

include conditions related to pituitary impairment such as hypophysitis, hypopituitarism, and adrenocorticotrophic hormone deficiency as adverse drug reactions.

Indications of nivolumab includes malignant melanoma, unresectable advanced or recurrent non-small cell lung cancer and relapsed or refractory classical Hodgkin lymphoma. Also, nivolumab is used for chemotherapy to treat unresectable, advanced or recurrent gastric cancer that has progressed after initial cancer chemotherapy.

A total of 76 cases involving pituitary impairment have been reported in Japan during the previous three fiscal years. Of the 76 cases, a causal relationship with the product could not be excluded for 11 cases. Also, two patient mortalities have been reported, including one case for which a causal relationship with the product could not be excluded.

MHLW and PMDA advise that patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of use should be taken.

Reference:

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

Opioid pain medicines

Risk of uncontrolled pain and withdrawal symptoms following sudden discontinuation

USA. The US Food and Drug Administration (FDA) has required changes to the prescribing information for opioid pain medicines to warn of serious withdrawal symptoms, uncontrolled pain, psychological distress and suicide following sudden

discontinuation or a rapid decrease in dose.

Opioids are used to manage pain when other analgesic treatments cannot be taken or are not able to provide enough pain relief. Common opioids include codeine, fentanyl, hydrocodone, morphine and oxycodone.

Rapid discontinuation can result in uncontrolled pain or withdrawal symptoms. Patients may attempt to treat their pain or withdrawal symptoms with illicit opioids, such as heroin and other substances.

Health-care professionals should not abruptly discontinue opioids in a patient who is physically dependent. When health-care professionals and their patients have agreed to taper the dose of an opioid analgesic, a variety of factors should be considered which include: the dose of the drug, the duration of treatment, the type of pain, and the physical and psychological attributes of the patient.

There are no standard opioid tapering schedules that are suitable for all patients. A patient-specific plan should be created to gradually taper the dose of the opioid and patients should be monitored and supported to prevent serious withdrawal symptoms, worsening of pain or psychological distress.

Reference:

Safety Alerts for Human Medical Products, US FDA, 9 April 2019 (www.fda.gov)

Quetiapine

Risk of serious skin diseases

Japan. MHLW and PMDA have announced that the package insert for quetiapine (Seroquel® and Bipresso®) should be revised to include toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson

syndrome) and erythema multiforme as adverse drug reactions.

Quetiapine is indicated for schizophrenia and improvement of depressive symptoms in patients with bipolar disorder.

One case of TEN, one case of oculomucocutaneous syndrome, and one case of erythema multiforme have been reported in Japan during the previous three fiscal years, respectively. Of these three cases no patient mortalities have been reported.

Reference:

Revision of Precautions, MHLW/PMDA, 19 March 2019 (www.pmda.go.jp/english/)

Sodium-glucose co-transporter 2 (SGLT2) inhibitors

Risk of necrotising fasciitis of the perineum (Fournier's gangrene)

1. Singapore. The Health Sciences Authority (HSA) has announced that the package inserts for sodium-glucose co-transporter 2 (SGLT2) inhibitors are being updated to warn about the risk of necrotising fasciitis of the perineum (Fournier's gangrene).

SGLT2 inhibitors are oral glucose-lowering agents that increase the renal excretion of glucose through the inhibition of SGLT2-mediated renal glucose reabsorption. Three SGLT2 inhibitors have been registered in Singapore. They are canagliflozin (Invokana®), dapagliflozin (Forxiga® and Xigduo XR®), and empagliflozin (Jardiance® and Glyxambi®).

The HSA has not received any local reports of Fournier's gangrene associated with SGLT2 inhibitors.

Health-care professionals are encouraged to take into consideration this risk when prescribing a SGLT2 inhibitor and to consider the possibility of Fournier's gangrene in SGLT2 inhibitor-treated patients who present with pain, tenderness, erythema or swelling in the genital or perineal area.

Reference:

Product Safety Alerts, HSA, 9 May 2019 (<http://www.hsa.gov.sg/>)

2. Japan. MHLW and PMDA have announced that the package inserts for products containing SGLT2 inhibitors should be revised to include necrotising fasciitis of the external genitalia and perineum (Fournier's gangrene) as an adverse drug reaction.

One case of Fournier's gangrene has been reported in Japan during the previous three fiscal years. A causal relationship to the product could not be excluded in this case.

A disproportionality analysis using the WHO global database of Individual Case Safety Reports (ICSRs), VigiBase® shows a higher number of adverse reaction of Fournier's gangrene or necrotising fasciitis reported for multiple SGLT2 inhibitors than would be expected in the entire database. In addition, data from other antidiabetic drugs have not shown such a trend.

Although the mechanism of Fournier's gangrene with SGLT2 inhibitors has not been elucidated, the pharmacological effect of SGLT2 inhibitors cannot be excluded.

Reference:

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

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

Sorbitol, fructose (excipient)

Hereditary fructose intolerance

Japan. MHLW and PMDA have announced that the package inserts for intravenous injection products containing sorbitol or fructose as excipients should be revised to include warnings for careful administration in patients with hereditary fructose intolerance.

Sorbitol and fructose are used in various medicines as excipients. Also, fructose is a metabolite from sorbitol in the body.

Although the package inserts for intravenous injection products containing sorbitol or fructose as active ingredients already specify a contradiction in those at risk of hereditary fructose intolerance, other products containing sorbitol and fructose as excipients will also include these warnings.

This follows the decision of the European Medicines Agency (EMA) to contraindicate the use of intravenous injection products containing sorbitol or fructose as excipients in patients with hereditary fructose intolerance.

As the products investigated contain sorbitol or fructose as excipients and not as an active ingredient, it is difficult to obtain information on adverse reactions and patient mortalities in these products from reports in Japan.

Reference:

Revision of Precautions,
MHLW/PMDA, 19 March 2019
(www.pmda.go.jp/english/)

fumarate (Takecab®, Vonosap® and Vonopion®) should be revised to include toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme as adverse drug reactions.

Vonoprazan is indicated for gastric ulcer, duodenal ulcer and reflux esophagitis, and for adjunct therapy in *Helicobacter pylori* eradication.

Seven cases involving TEN have been reported with vonoprazan use in Japan during the previous three fiscal years, and of the seven cases one reported a fatality.

Twenty-two cases involving oculomucocutaneous syndrome have been reported in Japan during the previous three fiscal years, but no mortality has been reported. Seventy-five cases of erythema multiforme have been reported in Japan during the previous three fiscal years, but no mortality has been reported.

Reference:

Revision of Precautions,
MHLW/PMDA, 19 March 2019
(www.pmda.go.jp/english/)

Vonoprazan

Risk of serious skin diseases

Japan. MHLW and PMDA have announced that the package inserts for preparations containing vonoprazan

Alemtuzumab

Cardiovascular and immune-mediated adverse effects

Europe. The EMA has temporarily restricted the use of alemtuzumab. It should now only be started in adults with relapsing-remitting multiple sclerosis that is highly active despite treatment with at least two disease-modifying therapies or where other disease-modifying therapies cannot be used.

This restriction follows new reports of immune-mediated conditions and problems with the heart and blood vessels. The EMA has started a safety review for alemtuzumab (Lemtrada®) to investigate cardiovascular and immune-mediated adverse effects.

Alemtuzumab is indicated to treat adults with relapsing-remitting multiple sclerosis.

In addition to the restriction, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended an update of the product information for alemtuzumab to include information about the cases of immune-mediated conditions, problems with the heart, blood vessels, and severe neutropenia.

For patients being treated with alemtuzumab, vital signs should be monitored before and during intravenous infusion. Liver function tests should be carried out before and during treatment. Also, patients who develop signs of pathological immune activation should be evaluated immediately, and a diagnosis of haemophagocytic lymphohistiocytosis considered.

The EMA will evaluate all available data on the safety concerns and consider any additional measures necessary.

Reference:

EMA, 12 April 2019
(www.ema.europa.eu)

Belimumab

Risk of serious psychiatric events

United Kingdom. The MHRA has announced that clinical trials show an increased risk of depression, suicidal ideation, behaviour and self-injury in patients with systemic lupus erythematosus receiving belimumab (Benlysta®) compared with those receiving placebo.

Belimumab is a human IgG1 monoclonal antibody, specific for soluble human B-lymphocyte stimulator protein, used as add-on therapy in adults with active, autoantibody-positive systemic lupus erythematosus and a high degree of disease activity.

The increased risk of psychiatric events was observed in clinical studies that led to the approval of belimumab. Although an assessment found the benefits of belimumab outweigh the risks, as a condition of its licence, the marketing authorisation holder has requested to conduct a randomised, placebo-controlled clinical trial to evaluate all-cause mortality and pre-specified adverse events of special interest. The study is global and currently ongoing.

Health-care professionals are advised to carefully assess the risk of depression and suicide before belimumab is started, and monitor all patients for new or worsening signs of these risks during treatment.

Reference:

Drug Safety Update, MHRA, 16 April 2019 (www.gov.uk/mhra)

Fluoroquinolone antibiotics

Risk of aortic aneurysm and dissection

Australia. The Therapeutic Goods Administration (TGA) is investigating a rare but serious adverse event of aortic aneurysm and dissection associated with fluoroquinolone antibiotics.

Fluoroquinolones are broad-spectrum antibiotics that are active against both gram-negative and gram-positive bacteria. They include ciprofloxacin, norfloxacin and moxifloxacin in Australia.

The TGA's investigation follows conclusions and recommendations made by the US FDA and the EMA's PRAC. The TGA has not received any Australian reports of aortic aneurysm or dissection/rupture associated with the use of fluoroquinolones.

Reference:

Medicines Safety Update, TGA, 12 April 2019 (www.tga.gov.au)

(See WHO Pharmaceuticals Newsletter No.2, 2019: Risk of aortic aneurysm and dissection in Singapore; No.1, 2019: Risk of aortic aneurysm and aortic dissection in Japan; No.6, 2018 Potential risk of aortic aneurysm and dissection in UK)

Insomnia medicines

Risk of serious injuries

USA. The FDA has announced that rare but serious injuries have occurred with some medicines used to treat insomnia such as: eszopiclone (Lunesta®), zaleplon (Sonata®) and zolpidem (Ambien®).

The injuries are a result of sleep behaviours which include: sleepwalking, sleep driving and engaging in other activities while not fully awake. These complex sleep behaviours have also resulted in deaths.

Eszopiclone, zaleplon and zolpidem are medicines used to treat insomnia in adults who have difficulty falling asleep or staying asleep. They are a class of sedative-hypnotics and they work by slowing activity in the brain to allow sleep.

Health-care professionals should not prescribe eszopiclone, zaleplon or zolpidem to patients who have previously experienced complex sleep behaviours after taking any of these medicines. Also, health-care professionals should advise all patients that although rare, those behaviours have led to serious injuries or death and that if patients experience an episode of complex sleep behaviour, they should discontinue taking the medicines.

Reference:

Safety Alerts for Human Medical Products, US FDA, 30 April 2019 (www.fda.gov)

(See WHO Pharmaceuticals Newsletter No.5, 2014: Next day impairment in Australia; No.4, 2014: Reminder of risk of impaired driving ability the next day in Europe; No.3, 2014: Can cause next-day impairment in USA; No.1, 2014: New dosage recommendations to minimize risk of next-day impairment in both women and men in Canada; No.4, 2013: Lower recommended doses required in USA; No1, 2013: Lower recommended doses required in USA; No.4, 2012)

Tofacitinib

Increased risk of blood clots in lungs and death

Europe. The EMA has announced that the recommended dose of tofacitinib (Xeljanz®) should not be exceeded when treating rheumatoid arthritis due to an increased risk of blood clots in the lungs and death.

Tofacitinib is indicated to treat adults with moderate to severe rheumatoid arthritis, psoriatic arthritis and adults with moderate to severe ulcerative colitis.

An ongoing study in patients with rheumatoid arthritis provided preliminary results showing an increased risk of blood clots in the lungs and death when the normal dose of 5mg twice daily was doubled. The aim of the study was to investigate the risk of heart and circulatory problems with tofacitinib in patients 50 years or older with at least one additional cardiovascular risk factor and to compare its safety with that of another medicine called tumour necrosis factor (TNF) inhibitor.

While full results of the investigation are pending the EMA recommends that health-care professionals monitor patients for signs and symptoms of blood clots in the lungs. Patients should not stop or change their dose of tofacitinib without talking to their doctor.

Reference:

EMA, 20 March 2019 (www.ema.europa.eu)

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

Yellow fever vaccine

Risk of fatal adverse reactions

United Kingdom. The MHRA has announced that they have received two reports of fatal adverse reactions following exposure to the yellow fever vaccine (Stamaril®).

Yellow fever vaccine is indicated for active immunization against yellow fever.

The MHRA previously announced that live attenuated vaccines should not be given to people who are clinically immunosuppressed because live vaccine strains can replicate and cause an extensive, severe, and sometimes fatal infection.

Recently, the MHRA has been notified of two fatal adverse reactions to yellow fever vaccine. In one case, the vaccine was given to a person with a history of thymectomy following a thymoma. In another case, the vaccine was given to a 67-year-old with no other known risk factors. Both patients died shortly after the vaccination due to suspected yellow fever vaccine-associated viscerotropic disease.

Yellow fever vaccine-associated viscerotropic disease is a recognised adverse reaction that resembles severe yellow fever infection. The global reporting rate is approximately one case in every one million people vaccinated, and the risk is increased in individuals with thymus disease, immunosuppression and in those who are of the age of 60 years and older. Another serious risk of vaccination is vaccine-associated neurotropic disease, which can occur at a similar rate and with the same risk factors.

Due to a higher risk of severe and potentially fatal adverse reactions, yellow fever vaccine should only be given to people aged 60 years and older when it is considered that there is a significant and unavoidable risk of acquiring yellow fever infection. Any health-care professional must ensure they are fully familiar with the up-to-date Summary of Product Characteristics.

The MHRA is in the process of reviewing the benefit-harm balance of yellow fever vaccine, and the measures used to minimise risks, taking into consideration these reported cases and the latest scientific data.

Reference:

Drug Safety Update, MHRA, 16 April 2019 (www.gov.uk/mhra)

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

The signals in this Newsletter are based on information derived from reports of suspected adverse drug reactions available in the WHO global database of individual case safety reports (ICSRs), VigiBase. The database contains over 18 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC's current routine signal detection process. International pharmaceutical companies, when identified as uniquely responsible for the drug concerned, are invited to comment on the signal text. Signals are thereafter communicated to National Pharmacovigilance Centres, before being published in this Newsletter. Signal texts from UMC might be edited to some extent by WHO and may differ from the original version. More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 20). 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.

Desloratadine and the risk of experiencing dry eyes

Sarah Watson, Uppsala Monitoring Centre and Dr. Eugène van Puijenbroek, the Netherlands Pharmacovigilance Centre Lareb

Summary

Reports of the antihistamine desloratadine causing dry eyes in several patients worldwide have been shared in VigiBase, the WHO global database of individual case safety reports. Anticholinergic effects of antihistamines as a group are known, but this specific adverse drug reaction is not labelled, and the drug might be overlooked as a potential cause of the reaction.

Introduction

Desloratadine is a long-acting, non-sedating histamine antagonist with selective peripheral H₁-receptor antagonist activity. It is indicated in adults and children aged one year and above for allergic rhinitis (among which hay fever is one type) and urticaria. In patients with allergic rhinitis, desloratadine is effective in relieving symptoms such as sneezing, nasal discharge and itching, as well as ocular itching, tearing and redness, and itching of palate.¹ Dry eye occurs when the surface of the eye is inadequately lubricated due to a decreased quantity and/or quality of tears. Symptoms include itching, stinging or burning, excess tears following periods of dryness, pain, and redness in the eye. People with dry eyes may also experience blurred vision.²

Reports in VigiBase

There were 13 reports (after removal of a likely duplicate) of the MedDRA preferred term *dry eye* for desloratadine in VigiBase, the WHO global database of individual case safety reports, as of May 2018. The reports originated from Canada, Finland, Norway, Portugal, Sweden, Switzerland and the USA. Of the 13 reports, nine had desloratadine as the only suspected drug for the reaction. The time to onset was recorded in eight cases; the same day in three reports, "within a few days" in one, "since start of treatment" in one, and 14 days, one month and six months, respectively in the three other reports. The age distribution ranged from two to 75 years, and ten of the reports concerned female patients. Based on the overall reporting of adverse reactions for desloratadine and on the adverse reaction dry eye on its own in VigiBase, 5.2 reports were statistically expected for the drug-adverse drug reaction (ADR) combination based on the disproportionality measure (IC). As there are more reports of desloratadine as well as for dry eyes in general for females, the relatively high number for females in this case series was not unexpected. In six of the reports there was a documented effect upon withdrawal of the drug; the reaction abated in all cases (one when the dose was decreased) and in the two cases where the drug was reintroduced, the reaction reoccurred. In four cases dry mouth/oral dryness was co-reported and other co-reported terms included dry skin, dry nose, chapped lips and vaginal dryness, all of

which could indicate that those patients had multiple anticholinergic adverse reactions to the drug. In one of the reports where the reaction occurred on the same day as the drug was introduced, the reaction was experienced within 2-3 hours and the patient experienced dry eyes, blurred vision and partial visual loss resulting in problems focussing on digital screens and driving their car.

Literature and Labelling

No adverse drug reactions for eyes are listed in the product label for desloratadine, but dry mouth which could indicate anticholinergic properties of the drug, is listed as a common ADR.^{3,4} Adverse anticholinergic effects include among other reactions: dry mouth, constipation, urinary retention, bowel obstruction, dilated pupils, blurred vision, increased heart rate and decreased sweating.⁵ The relative anticholinergic effect of different antihistamines has been shown by Orzechowski et al. in guinea pigs where desloratadine showed anticholinergic properties and to a larger extent than both diphenhydramine and loratadine both in vitro and in vivo.⁶ Additionally, the ability of antihistamines such as desloratadine to interact with human muscarinic receptors was investigated in a study by Wolff et al. where they used in vitro cells stably expressing one of the five human muscarinic receptors (M1-M5). It was shown that desloratadine was a full antagonist at all five receptors, and the study concluded that several marketed antihistamines, of which desloratadine was one, possessed marked anticholinergic activity "with the potential to cause adverse ocular side effects such as dryness".⁷

Discussion and Conclusion

It is known that hay fever, which is one of the most common indications of desloratadine, may cause inflammation of the conjunctiva and is an alternative cause to eye discomfort experienced during the pollen season.⁸ However, the reports with a rapid time to onset after drug administration point to a causal relationship with the drug. The small number of reports in VigiBase might be because it is not a serious reaction and that not all

patients would report such complaints. However, dry eyes could be perceived as both painful and incapacitating, affecting both the ability to focus on digital screens and to drive, as has been described in one of the reports in VigiBase. Based on the anticholinergic properties of desloratadine and strengthened by the reports with a short time to onset and both de- and rechallenges in VigiBase, this is likely to be an overlooked anticholinergic adverse drug reaction that should be considered for inclusion in the product labels and patient leaflets.

References

1. UKeMC SPC for Desloratadine. Available from: <https://www.medicines.org.uk/emc/product/4888/smpc>. Access date: Apr 2018.
2. National Eye Institute, National Institutes of Health Available from: <https://nei.nih.gov/health/dryeye/dryeye>. Access date: May 2018.
3. UKeMC PIL for desloratadine. Available from: <https://www.medicines.org.uk/emc/files/pil.4888.pdf>. Access date: Apr 2018.
4. US DailyMed PIL. Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=dbb8e695-f00b-4c67-bd49-09a1ae5bb669&audience=consumer>. Access date: Apr 2018.
5. Lieberman A. Managing Anticholinergic Side Effects. *Prim Care Companion J Clin Psychiatry*. 2004; 6(suppl 2): 20-23.
6. Orzechowski RF1, Currie DS, Valancius CA. Comparative anticholinergic activities of 10 histamine H1 receptor antagonists in two functional models. *Eur J Pharmacol*. 2005 Jan 4;506(3):257-64. Epub 2004 Nov 30.
7. Wolff S.C, Brubaker K, Navratil T, Fulcher E.H, Lankford J.R and Boyer J.L. Anticholinergic Effects of Antihistamine Drugs Used in the Clinic. *Journal of allergy and clinical immunology*. 2007 Jan 119 (1), Supplement, page s 153.
8. Kumar N, Feuer W, Lanza N.L and Galor A. Seasonal Variation in Dry Eye. *Ophthalmology*. 2015, August; 122(8): 1727-1729.

Etanercept and ophthalmic herpes

Sarah Watson, Uppsala Monitoring Centre and Dr. Eugène van Puijenbroek, the Netherlands Pharmacovigilance Centre Lareb

Summary

Adverse reactions of etanercept such as opportunistic infections and eye inflammation are mentioned in the patient information leaflet and herpes zoster is included in the label. The risk of acquiring a herpes infection in the eye and the potential severity of that infection is however not mentioned in the patient information leaflet of etanercept. Information about the risks of ophthalmic herpes is important for an early diagnosis, as more severe forms of ophthalmic herpes can, if left untreated, permanently affect the eyesight.

Introduction

Etanercept is a human tumour necrosis factor receptor p75 Fc fusion protein produced by recombinant DNA technology in a Chinese hamster ovary mammalian expression system. It is indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, axial spondyloarthritis, ankylosing spondylitis and psoriasis.¹

Herpes zoster (shingles) is a common disorder in primary care and is caused by the Varicella-Zoster Virus (VZV). One fifth of the population, mainly elderly people, will present with this neurocutaneous infection during their lifetime. Most immunocompetent patients will experience spontaneous and complete recovery within a few weeks. Some, however, will develop complications such as post-herpetic neuralgia and, in cases of ophthalmic herpes zoster, sight-threatening eye problems.² A related DNA virus is Herpes Simplex Virus (HSV), that infects humans by direct contact of skin or of mucous membrane with lesions or secretions holding viruses. HSV type 1 is primarily responsible for orofacial and ocular infections and may cause ophthalmic herpes without the need for a primary ocular HSV infection. HSV type 2, which is generally transmitted sexually will only rarely infect the eye if orofacial contact is made with genital lesions, and is sometimes transmitted to neonates as they pass through the birth canal of a mother with an active genital HSV type 2 infection.³

Conjunctivitis is seen in nearly all ophthalmic herpes zoster patients. More severe disorders include keratitis, uveitis and optic neuritis. Untreated, these latter diagnoses might lead to permanently affected eyesight. Without an early diagnosis of ophthalmic herpes and subsequent antiviral treatment, about half of all patients will develop eye disorders of various kinds.² Both VZV and HSV may cause severe corneal infections. Although the pattern of the corneal manifestations differs, both types of herpes keratitis may result in

potentially devastating complications for which immediate ophthalmological treatment is needed.^{4,5} For HSV, as well as for HZV, the incidence of infections is increased in immunocompromised persons.⁶

Literature and Labelling

In the section for adverse reactions in the UK Summary of Product Characteristics for etanercept, herpes zoster is mentioned under serious infections; *"opportunistic infections have been reported in association with etanercept, including invasive fungal, parasitic (including protozoal) and viral (including herpes zoster)..."*. Herpes simplex is not mentioned in the label.¹ However, due to the immunosuppressive nature of etanercept, reactivation of this virus is not unlikely.

The patient information leaflet for the same product under "Serious side effects" states that you may need urgent medical attention if you show *"signs of nerve disorders, such as numbness or tingling, changes in vision, eye pain, or onset of weakness in an arm or leg"* and infections are listed as common. Under "Uncommon" side effects *eye inflammation* (not further specified) is given, and under "Rare" side effects *nervous system disorders (... inflammation of the nerves of the eyes...)* is listed.⁷ However, for a patient, this information might seem unspecific and may not be perceived as a sign of a potentially serious ophthalmological disorder, with the risk of permanent damage.

Reports in VigiBase

As of 3 May 2018, there were 50 reports of ophthalmic herpes for etanercept in VigiBase, the WHO global database of individual case safety reports. Based on the overall reporting of adverse reactions for etanercept and on the adverse reaction ophthalmic herpes on its own in VigiBase, 4.1 reports were statistically expected for the drug-adverse drug reaction (ADR) combination based on the disproportionality measure (IC). The reports originated from Europe and the US. Forty-five reports were classified as serious. Several ophthalmic disorders were co-reported, all in patients with a non-specified ocular herpes infection. These concerned a 39-year-old male with ulcerative keratitis, an 85-year-old female with a retinal haemorrhage, corneal scar and uveitis, a male, age not reported, who experienced a corneal graft rejection, a 48-year-old male with uveitis, corneal disorder and necrotising scleritis that needed a scleral patch graft, a consumer report

concerning a 60-year-old woman who co-reported cataract and glaucoma, a consumer report concerning a female of unknown age with glaucomatocyclitic crisis (Posner-Schlossman Syndrome) and finally one consumer report concerning a male, age not reported, with recurrent ophthalmic herpes resulting in a corneal scar outside visual field. With the exception of glaucomatocyclitic crisis, the co-reported terms may result either directly or indirectly from an ophthalmic herpes infection.

Of the 24 cases with a documented outcome, 13 reports stated that the patients had *Not Recovered* from the event at the time the report was submitted, one *Recovered with sequelae*, seven reported that they had *Recovered* and three were *Recovering* at the time of reporting. Some reports also describe the situation of the patients. In one case, the patient stopped the treatment on their own initiative, after a severe episode of cold sores in the mouth, nose and ears, which was co-reported with "cold sores in the eye". On the other hand, two patients are described as requesting continued treatment despite serious adverse reactions, since the treatment was working so well. One patient did not consider the ophthalmic herpes to be serious.

Conclusion

Although infections and eye inflammation are listed in the patient information leaflet for etanercept, without clear information about the risk of acquiring ophthalmic herpes and more specifically, the risks of leaving it untreated, there is a risk of permanent damage to the sight of the patients who are not treated in time.

References

1. electronic Medicines Compendium: Summary of Product Characteristics for etanercept (Benepali). Available from: <https://www.medicines.org.uk/emc/product/2708/smpc>. Accessed: May 2018
2. Opstelten W, Zaal MJ. Managing ophthalmic herpes zoster in primary care. *BMJ*. 16 Jul 2005;331(7509):147-151.
3. Wang JC. Herpes Simplex Virus (HSV) Keratitis. Available from: <https://emedicine.medscape.com/article/1194268-overview>. Accessed: June 2018.
4. Li JY Herpes zoster ophthalmicus: acute keratitis. *Curr Opin Ophthalmol*. 2018 Jul;29(4):328-333.
5. Kalezic T, Mazen M, Kuklinski E, Asbell P. Herpetic eye disease study: lessons learned. *Curr Opin Ophthalmol*. 2018 Jul;29(4):340-346.
6. JT Schiffer, L Corey. Herpes Simplex Virus. Ch 136 1943-62. AND RJ Whitley. Varicella-Zoster Virus. Ch 137 1963-69. In: Mandell, Douglas, and Bennett's Principles and Practice of infectious diseases. Edited by GL Mandell, JE Bennett, 7th ed. Churchill Livingstone Elsevier, Philadelphia 2010 ISBN-978-0-4430-6839-3.
7. electronic Medicines Compendium: Patient information leaflet for etanercept (Benepali). Available from: <https://www.medicines.org.uk/emc/files/pil.2708.pdf>. Accessed: May 2018.

Factor Xa inhibitors and haemospermia

A frightening, yet usually innocuous, adverse reaction

Kim Alting, the Netherlands Pharmacovigilance Centre Lareb and Ruth Savage, New Zealand

Summary

During a joint patient report signal detection screening involving the Uppsala Monitoring Centre (UMC) and the Netherlands Pharmacovigilance Centre Lareb, haemospermia in association with rivaroxaban and apixaban was identified. Based on the overall reporting of adverse drug reactions (ADRs) for rivaroxaban and of the adverse reaction haemospermia in VigiBase, the WHO global database of individual case safety reports, the expected value for the number of reports for the combination was 2.3 and the association was highlighted as disproportionately over-reported, by the information component (IC) analysis. A similar observation was made for apixaban, another Factor Xa inhibitor, and haemospermia where the expected number of reports was 0.7. In July 2018 VigiBase contained 39 case reports of Factor Xa inhibitors (rivaroxaban 28, apixaban 11) and haemospermia. The majority of the reports (80%) were from patients. Seven case reports described recovery on dechallenge. One patient experienced recurrence on rechallenge. In 12 reports one or more other medicines that can cause haemorrhage were co-suspect. Four patients had conditions or underwent procedures that may have caused haemospermia. Haemospermia is not listed in the UK Summaries of Product Characteristics (SPCs), the US FDA labels, related patient information or other available literature for rivaroxaban and apixaban. However, many other haemorrhages are known ADRs for Factor Xa inhibitors. Haemospermia has a big impact on the users, since it is frightening to experience this kind of symptom. The reaction is not preventable, but if it was described in the Patient Information Leaflet, it would be clearer to patients that it is a known ADR.

Introduction

A VigiBase, the WHO global database of individual case safety reports, screening for potential signals arising predominantly from patient reports was conducted by staff from the UMC and Lareb in April 2018. An association between direct oral Factor Xa inhibitors (apixaban and rivaroxaban) and haemospermia was identified during this screening.

Factor Xa inhibitors belong to a group of medicines called Direct Oral Anticoagulants (DOACs) which have been developed as an alternative to warfarin. Dabigatran, a Factor IIa inhibitor, also belongs to this group. Factor Xa is required to activate prothrombin (Factor II) to thrombin (Factor IIa) which ultimately leads to fibrin clot formation and activation of platelets by thrombin. Factor Xa

inhibitors therefore reduce clot formation.^{1,2} Directly linked to their mechanism of action is the risk of haemorrhages.

Haemospermia is the presence of blood in the ejaculate. Haemospermia in itself is not harmful and usually has a benign origin. Although it is often harmless, it is frightening and concerning for patients. A malignant cause of haemospermia is rare and occurs almost exclusively in men aged over 40 years. The commonest causes are prostate biopsy, post-radiation treatment for prostate cancer and prostatitis. Other causes that have been identified include benign and malignant disorders of the urogenital tract, urogenital infections including schistosomiasis and those that are sexually transmitted, vascular malformations, and congenital or drug-induced bleeding disorders. However, in many cases a cause is not found and the condition resolves spontaneously. Recommended investigations depend on the persistence of haemospermia, associated symptoms and the age of the patient.^{3,4} We describe here the clinical assessment of the reports in the identified Factor Xa and haemospermia combinations.

Reports in VigiBase

Based on the overall reporting of adverse drug reactions (ADRs) for rivaroxaban and of the adverse reaction haemospermia in VigiBase, the expected number of reports in the combination was 2.3, the observed number was 28, and the association was highlighted as disproportionately over-reported by the information component (IC) analysis. A similar observation was made for apixaban, another Factor Xa inhibitor, and haemospermia where the expected number of reports was 0.7 and the observed number 11. There were no reports of haemospermia for the other available Factor Xa-inhibitor edoxaban, however the total number of reports for this drug was low. For both the rivaroxaban and apixaban combinations patients contributed the majority of reports (80%).

In July 2018 VigiBase held 39 case reports for Factor Xa inhibitors (rivaroxaban 28, apixaban 11) and haemospermia, excluding duplicates. The reports originated from nine countries. Age was stated for 28 patients and ranged from 28 to 84 years, mean 63.5, median 67 years. The indications included 14 for cerebral vascular accident/thrombosis prophylaxis, 12 in combination with atrial fibrillation, one also with a pulmonary embolism. Other indications were atrial fibrillation (5), pulmonary embolism (5), deep vein thrombosis (DVT) (5), venous thromboembolism prophylaxis

(3), thrombophilia (1), unknown (6). The time to onset of haematospermia from starting the Factor Xa inhibitor in 17 case reports was within four months. In six other reports time to onset was less specific and ranged from within seven months to approximately three years, in one case triggered by a prostate biopsy. Time to onset was not reported for 16 patients. Daily dose was reported for 19 patients and only one, on apixaban, appeared to be taking greater than the recommended dose for their indication, although there was in most of the cases no information on renal function.

Rivaroxaban or apixaban were the sole suspect medicines in 28 reports. In two other reports the reviewers considered that ibuprofen and citalopram were co-suspect. In eight other reports one or more other medicines that can cause haemorrhage (i.e. acetylsalicylic acid, clopidogrel, selective serotonin reuptake inhibitors (SSRIs), and nonsteroidal anti-inflammatory drugs (NSAIDs)) were co-suspects. Documentation was poor to moderate in most of the case reports and it is possible that some information on confounders was missing. However, five patients had conditions or underwent procedures that may have caused haematospermia and the Factor Xa inhibitor may have exacerbated the bleeding. These were prostate cancer, prostatitis, prostatitis with prostate biopsy, prostate biopsy and transurethral resection of the prostate gland. The timing of the last two in relation to onset of haematospermia was unclear. Several other patients had prostatic enlargement and/or increased blood prostate specific antigen but it is unclear if these would have increased the possibility of haematospermia on anticoagulants. Seven reports were described as serious because of hospitalisation, but only one was for haematospermia alone. Four of these patients also reported a gastrointestinal haemorrhage. Although the remainder of the reports were not serious, three patients described anxiety, stopping sexual intercourse or consulting another physician because they could not be reassured.

For seven cases it is known there was a positive dechallenge. One patient experienced recurrence on rechallenge. One patient was rechallenged with no recurrence. Table 1 shows the case reports with a positive dechallenge for haematospermia in association with rivaroxaban or apixaban. For patient 2, recovery on dechallenge may have been coincidental with recovery from prostatitis and prostate biopsy.

An overview of antithrombotic agents (anticoagulants and antiplatelet agents) in VigiBase showed that, as for the oral Factor Xa inhibitors, haematospermia with the antiplatelet agents aspirin, ticagrelor and clopidogrel was also reported more often than expected and highlighted by the IC values. Patients contributed 33 to 57% of these reports. There is a published case report of clopidogrel and haematospermia with recurrence on rechallenge.⁵ In contrast, overall

reporting for haematospermia, including patient reporting, was low for the vitamin K antagonists (acenocoumarol, phenprocoumon, warfarin), the heparin group and dabigatran none of which were disproportionately over-reported based on IC values.

Literature and Labelling

Haematospermia is not listed in the UK Summary of Product Characteristics (SPC) or the FDA labels for rivaroxaban, edoxaban and apixaban or on the associated patient information. The less specific term urogenital bleeding is mentioned in the SPCs for apixaban and rivaroxaban and the rivaroxaban Patient Information leaflet (PIL). Urethral bleeding is mentioned in the edoxaban SPC but not the PIL and in the apixaban and edoxaban FDA labels but not the patient medication guides. However, many other haemorrhages are listed ADRs for Factor Xa inhibitors.^{2,6-10} Micromedex and Martindale also have no information on haematospermia in association with Factor Xa inhibitors except that Micromedex lists the less specific genital haemorrhage for apixaban. A literature search on PubMed using the following criteria found no articles: ("rivaroxaban"[MeSH Terms] OR "rivaroxaban"[All Fields]) OR ("apixaban"[MeSH Terms] OR "apixaban" [All Fields]) OR ("edoxaban"[MeSH Terms] OR "edoxaban" [All Fields]) AND ("hemospermia"[MeSH Terms] OR "hemospermia"[All Fields] OR "haematospermia"[All Fields]).

Discussion

There were 39 cases of haematospermia with rivaroxaban and apixaban in VigiBase at the time of analysis. This is a preliminary signal as the case reports were moderately to poorly documented, so there is limited information on time to onset and outcome of the adverse events. However, seven patients recovered on dechallenge and one experienced a recurrence on rechallenge although one had an alternative or contributory cause for the bleeding (Table 1). A striking feature of the case series is the high proportion of patient reports. There is no information on haematospermia in the UK SPCs of rivaroxaban, apixaban and edoxaban. The terms urogenital or urethral bleeding in the UK SPCs and FDA labels do not specifically indicate that haematospermia has been reported and even these terms only appear in patient information for edoxaban. There are also no articles in PubMed regarding haematospermia in association with Factor Xa inhibitors. However, the pharmacological mechanism is clear and haemorrhages from various sites are described in the SPCs and other sources.

The greater reporting of haematospermia with the Factor Xa inhibitors and, to a lesser extent, the antiplatelet agents compared with other antithrombotics could be explained by two hypotheses. One is that haematospermia can

occur with all antithrombotic (anticoagulant and antiplatelet) agents, and the prominence of reports with newer agents is due to greater reporting of all suspected ADRs in recent years, including patient reporting, as well as the well-known more intense reporting with newer agents which, in this case, includes the direct oral anticoagulants (DOACs) and the p2y12 inhibitors (e.g. clopidogrel and ticagrelor). Nevertheless, more intense reporting for newer agents might not apply to patients since to them it does not matter what medicine they started on, it is all new to the patient. An exception is the statistical prominence of haemospermia with aspirin and >50% patient reporting even though it is an old medicine. However, newer antithrombotics were co-suspects in almost 75% of the aspirin reports. This might explain why reporting for aspirin is more similar to the newer agents. Dabigatran is also a newer anticoagulant and the lower reporting of haemospermia with this medicine compared with the oral Factor Xa inhibitors is more difficult to explain. It could be due to the fact that bleeding from the penis is listed as a known ADR in the PIL for dabigatran.¹¹ The alternative hypothesis is that antiplatelet agents and Factor Xa inhibitors are more likely to cause haemospermia than other antithrombotic agents, but there is no apparent biologic plausibility for this selectivity.

Haemospermia usually has a benign origin. Personal communication suggests that men do not present frequently with antithrombotic-related haemospermia to urological or men's health clinics, suggesting that most are reassured by their general practitioners or cardiologists or that the condition is transient. Recommended investigations for haemospermia depend on its persistence, associated symptoms and the age of the patient.^{3,4} This approach should also apply to patients taking antithrombotic agents.

Haemospermia has a big impact on the users, since it is frightening to experience this kind of symptom, but most can be reassured. While patient information necessarily focuses on warning symptoms of serious bleeding, the patient reports of haemospermia in this case series are also a reminder of adverse reactions that are usually not serious but can be very disturbing to the patient. They suggest that it may be helpful to list such reactions, where evidence is considered sufficient, so that patients are aware that their medicine is a potential cause of their condition. Given the rare possibility of an underlying malignancy, however, haemospermia would have to be grouped with symptoms that merit consultation if the condition persists.

Conclusion

Haemospermia with the Factor Xa inhibitors rivaroxaban and apixaban was signalled through a patient reporting sprint based on reports in Vigibase. The signal is preliminary but there is

strong biologic plausibility. The signal highlights the problem of adverse reactions that are rarely serious but are very disturbing to patients. It may be helpful for patients to have haemospermia listed in patient information for rivaroxaban, apixaban and other antithrombotics, where there is sufficient evidence, so that they are aware it is a possible adverse reaction to their medicine.

References

1. Drugbank. Rivaroxaban. Available from: <https://www.drugbank.ca/drugs/DB06228>. Accessed: September 2018.
2. US Daily Med: Summary of Product Characteristics for rivaroxaban (Xarelto®). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=10db92f9-2300-4a80-836b-673e1ae91610>. Accessed: September 2018.
3. Up to date: Weiss BD, Richie JP. Hematospermia. Available from: <https://www.uptodate.com/contents/hematospermia/>. Accessed: June 2018.
4. Ahmad I, Krishna NS. Hemospermia. The Journal of Urology 2007; 177(5): 1613-1618.
5. Celik A, et al. Hematospermia due to clopidogrel: The unknown side effect. Blood Coagulation and Fibrinolysis 2015; 26(1): 113.
6. US Daily Med: Summary of Product Characteristics for apixaban (Eliquis®). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e9481622-7cc6-418a-acb6-c5450daae9b0>. Accessed: September 2018.
7. US Daily Med: Summary of Product Characteristics for edoxaban (Savaysa®). Available from: <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=e77d3400-56ad-11e3-949a-0800200c9a66&audience=professional>. Accessed: October 2018.
8. Electronic Medicines Compendium: Summary of Product Characteristics for rivaroxaban (Xarelto®). Available from: <https://www.medicines.org.uk/emc/search?q=rivaroxaban>. Accessed: October 2018.
9. Electronic Medicines Compendium: Summary of Product Characteristics for apixaban (Eliquis®). Available from: <https://www.medicines.org.uk/emc/search?q=apixaban>. Accessed: October 2018.
10. Electronic Medicines Compendium: Summary of Product Characteristics for edoxaban (Lixiana®). Available from: <https://www.medicines.org.uk/emc/search?q=%22edoxaban+tosilate%22>. Accessed: October 2018.

11. Electronic Medicines Compendium: Summary of Product Characteristics for dabigatran (Pradaxa®). Available from:

<https://www.medicines.org.uk/emc/files/pil.6229.pdf>. Accessed: October 2018.

Table 1. Characteristics of case reports in VigiBase of haematospermia in association with rivaroxaban and apixaban, with a positive dechallenge.

Case	Age	Reporter type	Suspected (S), concomitant (C) or interacting (I) drugs	Daily Dose DOAC* (mg)	ADR terms reported	Time to onset (TTO)	Dechallenge/Rechallenge	Outcome
Rivaroxaban								
1.	-	Physician	Rivaroxaban (S)	-	Haematospermia Neoplasm malignant Faeces discoloured Fatigue	-	Rivaroxaban withdrawn Rechallenge	Recovered except for neoplasm malignant. Recurrence on rechallenge
2.	67	Consumer	Rivaroxaban (S), Ciprofloxacin (S)	2.5 mg tabs, frequency unknown	Haematospermia Blood urine present Atrial fibrillation Lung infection Blood pressure systolic increased	2 years approximately	Rivaroxaban withdrawn	Recovered from haematospermia, lung infection and blood in urine. Ciprofloxacin indication was prostatitis. Heavy bleeding in urine and semen occurred after prostate biopsy
3.	76	Consumer	Rivaroxaban (S) Acetylsalicylic acid (S) Ascorbic acid (C) Diltiazem (C) Magnesium oxide (C) Vitamin B complex (C) Vitamin D (C)	-	Haematospermia Blood urine present Anxiety	9 days	Rivaroxaban withdrawn after 12 days	Recovered from haematospermia (and recovering from blood in urine). CT scan and cystoscopy unremarkable. Changed to apixaban, unclear if this was before or after recovery
4.	74	Consumer	Rivaroxaban (S) Adenosine (C) Bisoprolol (C) Hydrochlorothiazide (C) Lisinopril (C) Pantoprazole (C)	20 mg tabs, frequency unknown	Bloody semen Gastrointestinal bleeding	3 months for GI bleeding, unknown for haematospermia	Rivaroxaban withdrawn Report unclear if rechallenged with no recurrence or not rechallenged	Recovered from both (after 4 days for GI bleeding) No recurrence or No rechallenge.
Apixaban								
5.	50	Physician	Apixaban (S)	-	Haematospermia Off label use	-	Apixaban reduced to off-label dose	Recovered
6.	49	Physician	Apixaban (S)	-	Haematospermia	14 days	Apixaban withdrawn after 23 days	Recovered
7.	61	Consumer	Apixaban (S) Bisoprolol (C)	-	Haematospermia	Within one month	Apixaban withdrawn after 3 months	Recovered

*direct oral anticoagulant

Factor Xa inhibitors and haematospermia

A frightening, yet usually innocuous, adverse reaction

Response from Bayer

The Uppsala Monitoring Centre (UMC) and the Netherlands Pharmacovigilance Centre Lareb have identified 28 case reports reporting

haematospermia in relationship to treatment with rivaroxaban. It is suggested by the authors that it may be helpful to list such reactions, where

evidence is considered sufficient, so that patients are aware that their medicine is a potential cause of their condition.

Bayer has conducted a search of the relevant medical literature and the company safety and clinical databases to identify cases of haematospermia and potential relationship to treatment with rivaroxaban. Urogenital tract hemorrhage (including hematuria and menorrhagia) is listed in the Xarelto® product label since it has been observed in clinical trials with a common frequency. Within treatment-emergent adverse events of male genital tract bleeding, there were five events of haematospermia in patients treated with rivaroxaban and eleven events in the control groups. The pool of clinical trials (phase II and III) with Xarelto® (rivaroxaban) comprises 59,336 patients treated with rivaroxaban and 44,011 patients in control groups, respectively. Hence, haematospermia can be considered a very rare expression of urogenital bleeding, which is listed as adverse reaction in the Xarelto® labeling.

A search in the Bayer global safety database for MedDRA preferred term (PT) haematospermia and PT Semen discolouration reported in association to treatment with rivaroxaban yielded 57 case reports for PT haematospermia and seven case reports for PT Semen discolouration (red, reddish, brownish, pink tint in at least five of seven) until 09 November 2018. This translates into a reporting frequency of 2.6 per million patient years, as estimated based on sales. In at least eight of these cases information on abnormalities of the prostate gland was provided by the reporter either in medical history or as a concomitant disease, and in at least 12 cases macrohematuria has been reported, too. In only three cases positive dechallenge and in one case positive de- and rechallenge has been reported. However, in the latter (non-medically confirmed, non-serious case) no further information was provided by the reporter. Overall quality of reported information was low, e.g. 28 of 64 case reports (43.8%) lacked any medical confirmation of the reported

events. Case reports frequently included other bleeding events (e.g. gastrointestinal bleeding, hematuria). In only eight of 24 medically confirmed and serious case reports no event other than haematospermia was reported. All cases identified with MedDRA PT Semen discolouration were assessed as non-serious. In summary, cases reviewed do not indicate any substantial impact of the reported event on the benefit-risk balance for Xarelto® in the approved indications, neither regarding frequency, nor nature and severity of event.

Bayer agrees with the authors that occurrence of haematospermia deserves attention of a physician as it may be caused by underlying urogenital disease including malignancy in the male urogenital tract. Given the rarity of haematospermia as a possible representation of bleeding during anticoagulant use and the absence of any imbalance for this event in the safety profile of Xarelto® compared to other anticoagulants, the question whether specific mention of the event in the product labeling is warranted should, however, be viewed with caution. Placing undue emphasis on the expected but infrequent association with anticoagulant therapies might even have the contrary effect of sending false assurance and delaying appropriate diagnosis. Moreover, discontinuation of an anticoagulant without appropriate medical consultation is to be avoided since this could prevent a patient from taking a potential life-saving medication.

In Summary

Bleeding is an important identified risk with use of Xarelto®. Haematospermia, a very rare expression of urogenital bleeding, is considered listed for rivaroxaban and the existent SmPC is considered sufficient in this regard. Any occurrence and observation of haematospermia should lead to physician attention and initiation of adequate diagnostic workup.

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.

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

Updates on Smart Safety Surveillance (3S) activities in India and Thailand

Improved pharmacovigilance (PV) can facilitate access to new and innovative treatments, by contributing to a better understanding of these products and by addressing patient safety issues promptly.

Supported by the Bill and Melinda Gates Foundation (BMGF), WHO is promoting the Smart Safety Surveillance (3S) approach, to strengthen PV systems in Low and Middle-Income Countries (LMICs) that are introducing new health products, for the safe and effective use of these products.

Three priority health products are being used as pathfinders, to introduce and test the 3S approach: Rotavac (rotavirus vaccine) for the prevention of rotavirus diarrhoea in young children, in India; bedaquiline, a product used in MDR-TB and tafenoquine, for treating *P. vivax* malaria.

India:

WHO, in collaboration with the Medicines Healthcare Products Regulatory Agency (MHRA) worked with the Ministry of Health and Family Welfare of India (MoHFW) and Central Drugs Standard Control Organization (CDSCO) to form a PV strengthening work plan, following an initial baseline assessment using the WHO PV preparedness tool. The tool identified gaps in the PV system, so that resources could be “smartly” allocated to bridge these gaps. The 3S-focus in India was to link PV activities between different stakeholders, for data sharing, signal detection, risk assessment, risk management, risk communication, and benefit-harm evaluation for regulatory decision making.



A series of activities have been carried out to reach these goals and included four workshops in New Delhi India, in February, March, April and May 2019.

The first workshop concentrated on ICSR reporting from and the engagement with the regulators. The second workshop was dedicated to risk management plans, and periodic safety update reports. Regulators and representatives from market authorization holders (MAH) attended. Regulators learned how to assess documents developed by the MAHs, and representatives from MAH learned how to prepare the documents, for submissions to the regulators.

In the third workshop, representatives from the national PV Centre (PVPI), CDSCO, the national expanded programme on immunization (EPI), vaccine experts and members of sentinel sites for vaccines attended. Together they formed a signal review panel in which all stakeholders were involved. This exercise highlighted the value of integration. Signal detection was performed on national reports for adverse effects reported with Rotavac preparations. The first two workshops built competencies and the skills were put to test in the fourth workshop which was dedicated to benefit-harm assessment using the findings from the previous trainings.

To learn how other experienced regulators do signal detection and perform benefit-harm assessments, a study visit to the MHRA, UK was organized in June 2019. Senior experts from the Indian regulator (CDSCO) and the EPI programme could spend a few days observing MHRA colleagues, to gain valuable insight into PV processes and practices within the MHRA.

Thailand:

3S efforts in Thailand will focus on getting the country ready for a product such as tafenoquine. A tailored workplan, to strengthen the national PV system, was drawn by Thai FDA colleagues and later, finalised during a scoping mission, with WHO and MHRA staff. All activities will be carried out as one of two sub projects:

Sub-project 1: Developing and strengthening Thai pharmacovigilance system for tafenoquine by

- reviewing the current situation relating to safety monitoring within the malaria treatment
- strengthening reporting processes
- strengthening the capability of Thai FDA staff to analyse pharmacovigilance data, detect signals, and assess the benefit-risk of medicines
- developing a risk-based strategy for launching tafenoquine

Sub-project 2: Advancing the concept of 'reliance',

- by observing the processes of medicinal product approval in other Agencies,
- with a focus on tafenoquine and the assessment of its risk management plans.

Completed activities include a workshop in May 2019, on basic PV, to introduce the principles of PV concept within the national malaria programme. Malaria programme managers, representatives from the NGO, Medicines for Malaria Venture (MMV), and staff from the Thai FDA were trained by WHO experts on the importance of PV, detecting and reporting ADRs, understanding the types of ADRs, PV reference sources, causality assessment and signal detection. They were trained by a colleague from UMC, to 'navigate' the WHO global database of individual case safety reports, Vigibase, to review the data and extract information by events, age, drugs etc. MHRA colleagues covered the sessions on reporting methods and Principles of Communication. All sessions used a good mix of presentations and group activities, with hands-on exercises and case studies.



Next, WHO is organizing a training workshop on assessing risk management plans and periodic safety update reports. This is slated for early July, with the participation of experts from the Therapeutic Goods Administration (TGA), Australia and the MHRA. Tafenoquine, approved recently by the TGA, will be used as an example in elaborating these topics. A site visit to TGA, in August, will allow Thai FDA colleagues to observe these aspects in practice.