Danish Pharmacovigilance Update # 7

Volume 5
August
2014

Contents

News from the EU

News from the DHMA

News from the EU

Ferumoxytol (Rienso) – changed recommendations to reduce the risk of serious anaphylactic reactions

In spring 2014, the EU's Pharmacovigilance Risk Assessment Committee (PRAC) initiated an investigation into the possible risk of anaphylactic reactions from treatment with the intravenous (IV) iron preparation ferumoxytol compared to other IV iron products. See *Danish Pharmacovigilance Update, May 2014.*

Resulting from the review of ADR reports, the recommendations for using ferumoxytol will be restricted to reduce the risk of serious sensitivity reactions:

- Ferumoxytol is now contraindicated in patients with any known history of drug allergy, including sensitivity to other parenteral iron products.
- Ferumoxytol should be administered as an intravenous infusion over a minimum of 15 minutes and must not be injected directly.
- During infusion of ferumoxytol, patients should be placed in a recumbent or semi-recumbent position and should remain in that position for at least 30 minutes after the infusion has finished.
- Patients should be monitored closely for signs of hypersensitivity – including blood-pressure and heart rate monitoring during infusion and for at least 30 minutes after the infusion has finished. If any signs of anaphylaxis develop during infusion, administration should be stopped immediately.
- Patients should be instructed to tell their doctor/healthcare professional if they start feeling unwell.

Ferumoxytol should only be administered by staff trained to recognise and manage anaphylactic reactions and only when resuscitation facilities are immediately available.

The other recommendations for using intravenous iron preparations still apply. See *Danish Pharmacovigilance Update, May 2014.*

Relevant specialists have been informed about the updated advice by letter. The letter, which is in Danish, is also available on our website: *List of circulated DHPCs.*

At the DHMA, we have received no reports to the Danish adverse reaction database describing anaphylactic reactions in connection with ferumoxytol treatment.

News from the EU

Restrictions on the use of bromocriptine (Parlodel®) to inhibit lactation

The European Medicines Agency, EMA, has concluded the reassessment of the efficacy and risks of using bromocriptine to stop breast milk production (inhibition of lactation) in women who have given birth.

Based on the EMA assessment, the following recommendations for bromocriptine will apply throughout the EU:

- Only bromocriptine in strengths up to 2.5 mg should be used to inhibit lactation. Higher bromocriptine strengths (5 mg and 10 mg) should not be used for this indication.
- Bromocriptine should only be used to inhibit lactation if medically indicated – such as in case of intrauterine and perinatal death, neonatal death or HIV infection of the mother.
- Bromocriptine should not be used for the suppression of lactation which can be adequately treated with non-medical treatment and/or ordinary analgesics.
- Bromocriptine is contraindicated in patients with uncontrolled hypertension, hypertensive symptoms associated with pregnancy (including eclampsia, pre-eclampsia or pregnancy-induced hypertension), hypertension post-partum and in the puerperium.
- Bromocriptine is contraindicated for lactation inhibition and other non-life-threatening conditions in patients with coronary artery disease or other severe cardiovascular conditions and in patients with symptoms of psychiatric disorders and/or a history of psychiatric disorders.

It is recommended that the blood pressure is monitored in patients treated with bromocriptine, especially at the start of treatment. If hypertension, cardiovascular symptoms, severe, progressive, or persistent headache (with or without visual disturbance) or evidence of CNS toxicity develops, bromocriptine treatment should be discontinued and the patient evaluated promptly.

Background leading to assessment by EMA

The assessment was initiated in response to increasing reports of rare, but serious cardiovascular, neurological and psychiatric reactions in France. The EU's Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed all available data and has concluded that bromocriptine is efficient in lactation inhibition. However, a possible link between bromocriptine treatment and serious incidents such as heart attack, blood clots, seizures and psychiatric symptoms could not be ruled out.

In Denmark, bromocriptine is used to inhibit lactation to a very limited degree. Figures from the Register of Medicinal Product Statistics and the Medical Birth Registry show that fewer than 70 women bought bromocriptine in connection with birth in 2013.

News from the EU

EU's list of recommendations on safety signals

As part of routine surveillance of medicines in the EU, the Pharmacovigilance Risk Assessment Committee (PRAC) assesses signals of possible adverse reactions every month to determine whether further measures are needed to improve medicines safety.

The list of signals leading PRAC to recommend further measures is published on the website of the European Medicines Agency (EMA) every month.

Among the most important recommendations on safety signals from the PRAC meetings in June and July 2014 were:

- Dexmedetomidine – Infantile apnoeic attack.
- Enzalutamide – Myalgia.
- Fluoroquinolones – Retinal detachment.
- Mycophenolate mofetil – Bronchiectasis and hypogammaglobulinaemia
- Vildagliptin (including vildagliptin-metformin combination) – Interstitial lung disease
- Vildagliptin (including vildagliptin-metformin combination) – Rhabdomyolysis
- Bupropion – Pancytopenia

See EU's list of recommendations on safety signals:

June: *PRAC recommendations on signals.*
July: *PRAC recommendations on signals.*

Fluoroquinolones and risk of retinal detachment

The EU's Pharmacovigilance Risk Assessment Committee (PRAC) recommends that the summaries of product characteristics for antibiotics of the fluoroquinolone class for systemic use be updated to include a warning on vision disorders.

Background leading to the SPC update

The update follows a review of data from published studies and reports of suspected adverse reactions in Europe.

A causal relationship between fluoroquinolones and retinal detachment could neither be established nor excluded, but because retinal detachment is such a serious adverse reaction prompting immediate treatment, the summaries of product characteristics will be updated with a warning to advise users to consult an eye specialist immediately if their eyesight becomes impaired or otherwise affected.

Ciprofloxacin, moxifloxacin and levofloxacin are fluoroquinolones authorised in Denmark for systemic use.
See the EU's list of signals for more details: *PRAC recommendations on signals.*

Focus on bleeding in patients treated with non-vitamin K antagonist oral anticoagulants

Introduction

At the DHMA, we routinely monitor the safety of Pradaxa® (dabigatran etexilate), Xarelto® (rivaroxaban) and Eliquis® (apixaban) also known as non-vitamin K antagonist (non-VKA) oral anticoagulants. As part of these monitoring activities, we perform a detailed review of the reports that are registered in the DHMA adverse reaction database. In addition, we collaborate with the Thrombosis Research Unit at Aalborg University Hospital, which provides us regularly with knowledge about potential safety problems, and the Danish National Agency for Patients' Rights and Complaints, which contributes with safety knowledge based on their review of reported adverse events.

The latest review and analysis of data are based on the reports of adverse reactions and adverse events that concern patients who experienced adverse reactions in the form of severe bleeding. Excluded in this review are, however, reports of adverse reactions and adverse events related to patients receiving preventive treatment for venous thromboembolism prior to hip and knee alloplasty.

The following safety problems were identified:

- Concomitant treatment with low-molecular weight heparins
- Problems with co-administration of warfarin and non-VKA oral anticoagulants
- Sudden decline in renal function in elderly patients
- Temporary discontinuation of treatment prior to surgery and invasive procedures

In the following, we go through the problems one by one with examples of reports of adverse reactions and adverse events.

Concomitant treatment with low-molecular weight heparins

In February 2014, the DHMA received a report describing a serious brain haemorrhage in a patient who continued to receive a low-molecular weight heparin when treatment with Xarelto® was started. In connection with this incident, the DHMA called attention to the fact that treatment with low-molecular weight heparin must be discontinued before initiating treatment with non-VKA oral anticoagulants. Read the warning on the DHMA website in Danish: *Sundhedsstyrelsen advarer om blodfortyndende medicin (The DHMA warns against blood-thinning medicines).*

The Danish National Agency for Patients' Rights and Complaints received a similar report about an adverse event describing a patient who in connection with surgery was taken off Pradaxa® temporarily and treatment with a low-molecular weight heparin was initiated. After surgery, the patient resumed Pradaxa® treatment, but the treatment with the low-molecular weight heparin was not discontinued, which led to major gastrointestinal bleeding.

According to the summary of product characteristics, concomitant treatment with low-molecular weight heparins is contraindicated in patients who are treated with non-VKA anticoagulants.

The three new oral anticoagulants are characterised by being quick-acting, and therefore no overlapping treatment is to be given when switching from other anticoagulants.

When switching from a low-molecular-weight heparin to a non-VKA anticoagulant, the treatment with the low-molecular-weight heparin must be stopped.

Treatment with Eliquis® can be initiated at the time when the next dose of low-molecular-weight heparin was to be given. Xarelto® and Pradaxa® can be initiated up to two hours before this time.

Problems with co-administration of warfarin and non-VKA oral anticoagulants

Both reports of adverse reactions and reports of adverse events have been submitted. They involve patients who, due to prescription errors, are treated with both warfarin and a non-VKA oral anticoagulant. The DHMA has received an ADR report concerning a switch from the vitamin K antagonist Marevan® to Xarelto®. By mistake, treatment with Marevan® was not discontinued, and the day after administration of Xarelto®, the patient suffered a serious brain haemorrhage.

The Danish National Agency for Patients' Rights and Complaints has received several reports about adverse events where patients, by mistake, were prescribed Marevan® and Xarelto® concomitantly. In some cases, the error was discovered before the patient sustained any injuries, but in one case the patient's INR levels increased and hospitalisation was prolonged.

According to the summary of product characteristics, concomitant use of warfarin and non-VKA anticoagulants is contraindicated. Since co-administration of these drugs could have serious consequences for patients, the prescriber should pay special attention to whether or not any previously prescribed warfarin has been discontinued before commencing treatment with a non-VKA oral anticoagulant.

Sudden decline in renal function in elderly patients

The DHMA has received several reports about Pradaxa® where elderly patients (> 75 years) suffered severe bleeding, which could be related to a sudden decline in renal function.

In elderly patients, doctors should be particularly aware of clinical situations such as hypovolemia, gastroenteritis, vomiting and dehydration, which could lead to a decline in renal function with resulting higher concentrations of anticoagulant in the blood. In elderly patients, a simple infection could cause dehydration and a subsequent decline in renal function, in which case the renal function must be monitored and the anticoagulant dose reduced as needed to avoid severe bleeding in the patient.

The Danish Society of Cardiology recommends that patients who begin treatment with a non-VKA oral anticoagulant have their renal function assessed every three months in the first year and subsequently once a year. In addition, the renal function should be assessed in special clinical situations whenever a decline in renal function is suspected. Renal function should be assessed by calculating the creatinine clearance, e.g. estimated glomerular filtration rate (GFR).

According to the summary of product characteristics, treatment with Pradaxa® should be discontinued if the creatinine clearance falls below 30 ml/min. Xarelto® and Eliquis® are not recommended if creatinine clearance is below 15 ml/min.

Precautions before surgery and invasive procedures

The Danish National Agency for Patients' Rights and Complaints has received a report about an adverse event involving an elderly patient who in connection with hip fracture surgery experienced major bleeding. The bleeding could not be managed surgically due to decreased coagulability, which was ascribed to Pradaxa® treatment. The patient died afterwards. Serum creatinine levels showed that the patient's renal function was impaired, and Pradaxa® was not adequately discontinued before surgery. In this particular case, only 24 hours passed between administration of the last Pradaxa® capsule and surgery, which is less time than recommended.

The Danish Society of Cardiology has prepared the guidelines below for temporary discontinuation before planned invasive procedures.

The table offers guidelines, and other factors can be taken into account, including clinical factors relevant to the risk of bleeding.

Length of temporary discontinuation (in hours) for new oral anticoagulants relative to renal function (estimated glomerular filtration rate, eGFR) and risk of bleeding (Low or High) in connection with planned invasive procedures.						
	Pradaxa®		Eliquis®		Xarelto®	
eGFR (mL/min)	Low	High	Low	High	Low	High
>50	≥ 36	≥ 72	≥ 24	≥ 48	≥ 24	≥ 48
30-50	≥ 48	≥ 96	≥ 24	≥ 48	≥ 36	≥ 72
15-29	Contraindicated		≥ 36	≥ 48	≥ 36	≥ 72
<15	Use of new oral anticoagulants are contraindicated					

Conclusion

The latest review of reported adverse reactions and adverse events focused on serious bleeding in particular. The review identified problems of concomitant treatment with a non-VKA oral anticoagulant and a low-molecular-weight heparin as well as co-administration of warfarin and a non-VKO oral anticoagulant. In addition, ADR reports were received describing severe bleeding in patients caused by a sudden decline in renal function which meant that the patients were especially sensitive to the drugs' anticoagulant effect. Finally, an adverse event was reported describing inadequate discontinuation of anticoagulant prior to planned surgery, which had a fatal outcome.

At the DHMA, we will be following the development and continue our close collaboration with the Danish National Agency for Patients' Rights and Complaints and the Thrombosis Research Unit at Aalborg University Hospital.

Since there has been a general increase in reports of adverse events involving anticoagulants, the Danish National Agency for Patients' Rights and Complaints will put increased focus on these drugs in the time ahead. Among other things, the work will be concluded by a publication.

Previous status reports and articles on the safety monitoring of non-VKA oral anticoagulants from the DHMA

Over the last couple of years, the DHMA has monitored the safety of non-VKA oral anticoagulants closely, and new and important knowledge has been published regularly. Below, you will find the previously published status reports, articles and warnings about adverse reactions and ADR reports. Not all information is available in English.

- DHMA website 15 March 2012: *First results from new study of Pradaxa® (dabigatran etexilate) – in Danish only*
- DHMA website 15 May 2012 (Danish version published 3 May 2012): *Pradaxa – consider age and follow dose recommendations*
- DHMA website Danish Pharmacovigilance Update, 20 September 2012: *Decline in the number of elderly people over 79 years of age receiving Pradaxa 150 mg*
- DHMA website 17 January 2013: *News about Pradaxa® (dabigatran etexilate) and Xarelto® (rivaroxaban) – in Danish only*

- Journal of the American College of Cardiology June 2013: *Efficacy and Safety of Dabigatran Etexilate and Warfarin in "Real-World" Patients With Atrial Fibrillation: A Prospective Nationwide Cohort Study*
- DHMA website 18 December 2013: *Patients with mechanical heart valves not to be treated with new oral anticoagulants – in Danish only. Warning was also sent to the Danish regions directly*
- DHMA website 11 February 2014: *DHMA issues warning about blood thinners – in Danish only*
  In this warning, the DHMA advises physicians to discontinue other anticoagulant therapy before starting treatment with the new oral anticoagulants.
- The American Journal of Medicine April 2014: *Myocardial Ischemic Events in ´Real World´ Patients with Atrial Fibrillation Treated with Dabigatran or Warfarin*
- The American Journal of Medicine July 2014: *Bleeding Events New Starters and Switchers to Dabigatran Compared with Warfarin in Atrial Fibrillation*

All cases referred to in this article originate from the Danish Health and Medicines Authority's database of adverse drug reactions. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, pharmaceutical companies should not report these cases to the Danish Health and Medicines Authority.

Risk of central serous chorioretinopathy in glucocorticoid treatment

By Farah Arif and Michael Larsen, Department of Ophthalmology, Glostrup Hospital

Glucocorticoid treatment is a significant risk factor for developing the disease known as central serous chorioretinopathy. Central serous chorioretinopathy (CSC), or simply central serous retinopathy, is a prevalent retinal disorder characterised by collection of fluid under the retina caused by a leakage in the blood vessels of the choroid underneath the retina. It is estimated that more than 500 people develop this disease every year in Denmark. It occurs in early adulthood and into the 70s, the incidence rate being highest at around the age of 45. The disease is more common in men than women.

Glucocorticoids are important and sometimes indispensable in medical treatment of a number of disorders. The treatment is prescribed by physicians across all specialties, which makes it important to raise awareness about CSC as a possible adverse reaction to corticosteroid treatment.

Use of inhalation steroid, nasal spray and ointment can also trigger CSC

A modest dose of glucocorticoids is enough to develop CSC, which makes it more a case of idiosyncrasy than a predictable dose-related adverse reaction. A molecular genetics study at Glostrup Hospital has shown a causal relationship with a gene variation responsible for keeping together the endothelium cells that line the inside of the choroid blood vessels. Therefore, it is important to be aware that CSC can also be induced by inhalation steroid, nasal spray or ointment.

Other risk factors for CSC

Another significant risk factor for development of CSC is psychosocial stress as manifested by the body's increased production of corticosteroids. In patients without such current risk factors, it sometimes occurs that the first symptoms manifest themselves in connection with impending divorce, unemployment or bankruptcy. In about half of the patients, no such risk factors can be identified.

CSC is increasingly being diagnosed because new methods for eye imagery have made it easier to identify the disease.

Many CSC cases reverse – usually without any permanent effects on the vision.

Recommendations for doctors:

- If a patient complains about blurred or distorted vision, he or she should be referred to an eye specialist for additional examination within 48 hours as this could be suggestive of subretinal neovascularization induced by CSC or another primary disease. Blurred vision could be a grey spot in the middle of the visual field. The patient will often experience this as straight lines that are bending, or jumping lines and letters when reading a newspaper. Other symptoms of visual disturbance include weakened perception of contrasts and colours, so that saturated colours become dull and unsaturated like pastels.
- When CSC is verified, corticosteroid treatment should be discontinued. If the patient cannot do without the treatment, it should be discussed to what degree the eye disease can be controlled with other available treatment options.
- Accumulation of fluid lasting for three months or longer is associated with increasing retinal photo receptor loss and may lead to permanent visual impairment. In this case, it is recommended to commence treatment to restore the interaction between the pigmented epithelium and retina.

CSC is so far only described in the summaries of product characteristics of a few products. There is wide clinical experience among eye specialists which shows that CSC regularly occurs in relation to glucocorticoid exposure, which is why it is considered a class effect in clinical practice.

Eye specialists who suspect cases of CSC to have been induced by glucocorticoid treatment are asked to report it to the Danish Health and Medicines Authority via *www.meldenbivirkning.dk* (report a side effect). In order for the DHMA to review the reports most efficiently, it is important to include in the report any other possible or likely causes of CSC such as stress or if the patient is treated systemically with glucocorticoids.

Leflunomide (Arava®) and polyneuropathy

The DHMA has received an ADR report about a middle-aged woman who was treated for 14 months with leflunomide for rheumatoid arthritis.

She developed signs of polyneuropathy with a sleeping, prickling sensation, primarily symmetrically, in her fingers and toes. For a longer period of time (16 months), the woman was treated concomitantly with methotrexate. Both drugs were discontinued. We have not yet received any information about the current well-being of the woman.

Doctors should be aware of the following:

- Several reports of peripheral neuropathy concern patients treated with leflunumide. In some patients, neuropathy subsided after discontinuation of the medicine, but other patients experienced persistent symptoms.

The DHMA has received a total of five reports that describe polyneuropathy as a possible adverse reaction to leflunomide.

- Concomitant treatment with neurotoxic medicine, such as leflunomide, and antidiabetics could increase the risk of neuropathy in patients over the age of 60 years.

- If a patient treated with leflunomide develops peripheral neuropathy, it should be considered to stop the treatment and commence the washout procedure[1].

- When switching from leflunomide to another "Disease-Modifying Antirheumatic Drug" (DMARD) (e.g. methotrexate), the washout procedure should be initiated because leflunomide has a long half-life and therefore could increase the risk of neuropathy even long after the switch to another product.

- Recent or concurrent treatment with hepatotoxic or haematotoxic drugs (e.g. methotrexate) may increase the risk of serious adverse reactions. Concomitant treatment is therefore not advisable, and closer monitoring of liver enzymes and haematological parameters is recommended in the initial phase after switching.

Indication for leflunomide
Leflunomide is indicated for the treatment of adult patients with:

- active rheumatoid arthritis as a "disease-modifying antirheumatic drug" (DMARD).
- active psoriatic arthritis.

[1]Washout procedure: Colestyramine 8 g is administered 3 times daily. Alternatively, 50 g of activated powdered charcoal is administered 4 times daily. Duration of a complete washout is usually 11 days. The duration may be modified depending on clinical or laboratory variables.

All cases referred to in this article originate from the Danish Health and Medicines Authority's database of adverse drug reactions. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, pharmaceutical companies should not report these cases to the Danish Health and Medicines Authority.

Danish Pharmacovigilance Update is published by
Danish Health and Medicines Authority
www.sundhedsstyrelsen.dk
Editor-in-Chief:
Henrik G. Jensen (HGJ)
Editor:
Nina Vucina Pedersen (NVP)
ISSN 1904-2086

Sundhedsstyrelsen
Danish Health and Medicines Authority