Danish Pharmacovigilance Update #7

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Cases of acquired haemophilia following treatment with clopidogrel (Plavix® etc.)

Cases of acquired haemophilia in association with the use of clopidogrel in persons with no history of abnormal haemostasis have been reported.

Worldwide, the reports comprised 11 cases of acquired haemophilia A and one case of acquired haemophilia B. Two cases were life-threatening, but non-fatal. The time to onset varied between the 12 cases and ranged from a few days to four months following start-up of treatment with clopidogrel.

Acquired haemophilia – a rare autoimmune disease

Acquired haemophilia is a very rare autoimmune disease with an incidence of approx. 1-4 patients per million per year. Morbidity and mortality are high due to the often high age of the patients, underlying diseases, bleeding and the toxic effect of immunosuppressant treatment.

Information on the risk of acquired haemophilia in association with the use of clopidogrel will now be added to the summary of product characteristics for medicines containing clopidogrel. See the product information (in Danish only) at *www.produktresume.dk*

As a doctor you should be aware of the following:

- Acquired haemophilia must be recognised immediately in order to minimise the risk of bleeding.
- In case of confirmed isolated activated partial thromboplastin time (APTT) prolongation with or without bleeding, acquired haemophilia should be considered.
- Patients with a confirmed diagnosis of acquired haemophilia should be treated by specialists, clopidogrel should be discontinued, and invasive procedures should be avoided.

The summary of product characteristics for clopidogrel will be updated as soon as possible, and letters of information have been sent to relevant doctors. DHPC letters are available on the Danish Health and Medicines Authority's website (in Danish only): *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals*

Indication for clopidogrel

Prevention of atherothrombotic events and prevention of athero-thrombotic and thromboembolic events in association with atrial fibrillation.

News from the EU

Change in indication and contraindication for panitumumab (Vectibix®)

Vectibix® is indicated for the treatment of adult patients with wild-type KRAS metastatic colorectal cancer (mCRC) in combination with chemotherapy containing oxaliplatin. However, this indication will now be changed due to the results of a new study.

The change is as follows:

- Patients should have wild-type RAS and not only wild-type KRAS mCRC. The contraindication will be extended to apply to all patients with mutant RAS or unknown RAS status.

New indication for Vectibix®:

Treatment of adult patients with wild-type RAS metastatic colorectal cancer (mCRC):

- As first-line treatment in combination with FOLFOX.
- As second-line treatment in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan).
- As monotherapy after failure of chemotherapy regimens containing fluoropyrimidine, oxaliplatin, and irinotecan.

New contraindication for Vectibix®:

The combination of Vectibix® with chemotherapy containing oxaliplatin is contraindicated in patients with mutant RAS mCRC and in patients with mCRC for whom the RAS status is unknown.

Letters of information and updated training material have been sent to relevant doctors. DHPC letters are available on the Danish Health and Medicines Authority's website (in Danish only): *List of issued DHPC letters (in Danish only)*

Review of medicines containing zolpidem

Zolpidem is used for short-term treatment of insomnia, and there is a risk of drowsiness and slower reactions the day after taking the medicine. This may increase the risk of accidents in situations which require increased alertness, such as driving.

Detailed analysis of the increased risk of accidents associated with the use of zolpidem required

In June, the European Medicines Agency, EMA, reviewed adverse reaction reports of problems with driving and road traffic accidents in patients receiving treatment with zolpidem. It was assessed that there is no immediate need to change the product information for medicines containing zolpidem. It was also discussed whether lower doses could reduce the risk of reduced mental alertness and impaired driving ability the day after taking zolpidem, and whether a dose reduction should be considered in certain groups of patients. The EMA concluded that a more detailed review and analysis of the benefits and risks associated with the use of zolpidem, including investigation of its efficacy at lower doses, is needed to decide this.

Therefore, the EMA has started such a review of medicines containing zolpidem.

Drowsiness the day after taking insomnia medicines

The possibility of drowsiness the day after taking medicine for the treatment of insomnia is a known risk, especially if patients do not sleep for long enough after taking the medicine.

See the product information for medicines containing zolpidem at *www.produktresume.dk* (in Danish only).

Read more about the review on the EMA's website. *Review of zolpidem-containing medicines started*

News from the EU

European Medicines Agency recommends suspension of medicines containing ketoconazole for oral use

An EU-wide review of medicines containing ketoconazole for oral use concluded that the risk of hepatic injury outweighs the benefits in treating fungal infections. Therefore, the European Medicines Agency, EMA, recommends suspension of medicines containing ketoconazole for oral use throughout the EU.

As a doctor you should be aware of the following until suspension:

- Doctors should no longer prescribe tablets containing ketoconazole.
- It should be considered whether patients on oral ketoconazole should stop treatment or switch to another treatment.
- Shampoos and creams containing ketoconazole have very low systemic absorption and may continue to be prescribed as currently approved.

The background for the new recommendation

All drugs in the same group of drugs as ketoconazole, the so-called azoles, carry a risk of hepatic adverse reactions. Data have shown that the incidence and seriousness of hepatic adverse reactions with oral ketoconazole are higher than with other antifungals.

In Europe, there has been several reports of serious hepatic adverse reactions including hepatitis, cirrhosis and hepatic failure with fatal outcomes or requiring liver transplantation following treatment with oral ketoconazole. The onset of the hepatic adverse reactions has most frequently occurred between one and six months after initiation of treatment, but has also been reported earlier than one month after initiation of treatment, and at the recommended dosing.

In addition, there are limited data from efficacy studies on oral ketoconazole.

The risk minimisation measures proposed, such as limiting the treatment duration or narrowing down the groups of patients, were not considered sufficient to reduce the risk of hepatic adverse reactions.

Indication for ketoconazole

Ketoconazole is an antifungal. In Denmark, ketoconazole is available for both oral treatment and topical treatment.

Read more in the EMA's press release: *European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole*

New recommendations for the use of painkillers containing diclofenac

New studies concerning medicines containing diclofenac have shown that there is a slight, but increased risk of cardiovascular adverse reactions similar to that seen with COX-2 inhibitor painkillers.

The European Medicines Agency, EMA, recommends to update the product information for medicines containing diclofenac based on European data on the risk of cardiovascular adverse reactions.

Therefore, the recommendations for medicines containing diclofenac have been changed to follow the recommendations for COX-2 inhibitors.

The new recommendations for the use of diclofenac:

- Diclofenac is contraindicated in patients with pre-existing heart disease or prior heart attack (ischaemic heart disease and/or left-sided heart failure (NYHA II-IV)), blood circulation disorder (peripheral arterial disease) and/or prior stroke or temporarily decreased blood supply to the brain (cerebrovascular disease).

- Patients with significant risk factors for development of heart disease (i.e. hypertension, elevated cholesterol levels, diabetes and smoking) should only be treated with diclofenac after careful consideration.

The new recommendations apply to all systemic formulations (i.e. tablets, prolonged-release tablets, suppositories and injection fluid), especially at high doses and during long-term treatment.

Indication for diclofenac
Diclofenac is used for the treatment of gout and other symptomatic hyperuricaemias.

Read the EMA's press release: *New safety advice for diclofenac – CMDh endorses PRAC recommendation*

News from the EU

Until further notice, plasma substitutes containing hydroxyethyl starch (HES) for volume replacement in case of blood or plasma loss should be avoided in critically ill patients – including patients with sepsis

In June 2013, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) completed a review of benefits and risks of the use of plasma substitutes containing hydroxyethyl starch (HES) for volume replacement in case of blood or plasma loss.

Increased risk of renal injury requiring dialysis

The review was initiated based on a number of new studies (see references 1,2,3) that compared HES with crystalloids for use in critically ill patients. The studies showed that patients with serious sepsis treated with HES had an increased risk of renal injury requiring dialysis. Furthermore, two of the studies suggested that mortality is increased in patients treated with HES.

The review comprised studying the scientific literature, data submitted by the companies and advice from a group of external experts in order to assess benefits and risks of treating blood or plasma loss with HES. The PRAC concluded that HES, when compared with crystalloids, increases the risk of renal injury requiring dialysis as well as mortality.

The PRAC recommends suspension of the marketing authorisations for medicines containing HES

The PRAC further concluded that the available data only showed a limited benefit of HES in plasma substitution and that the benefits therefore do not outweigh the known risks. Accordingly, the PRAC recommended suspension of the marketing authorisations for medicines containing HES, until the companies potentially identify a group of patients in whom the benefits of the medicines continue to outweigh the risks.

Marketing authorisation holders for HES products have appealed against the PRAC's recommendation

However, some of the marketing authorisation holders for HES products have appealed against this recommendation, and the final decision currently awaits the outcome of the appeal.

Until the final decision is available, the Danish Health and Medicines Authority (DHMA) recommends not to use HES in critically ill patients, including patients with sepsis, and to use HES with great caution in general.

Further information on the safety and precautions associated with the drugs is available in the product information at *www.produktresume.dk.*(in Danish only).

The DHMA encourages reporting of adverse reactions associated with the use of HES to the DHMA at *www.meldenbivirkning.dk*

1 Perner, A. et al. Hydroxyethyl Starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367(2):124-134.

2 Bunkhorst, F.M. et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med, 2008; 358(2):125-39.

3 Myburgh, J.A. et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care; N Engl J Med 2012; 367(20):1901-11.

4 As of July 2013, the following products are available on the Danish market: Hesra, HyperHAES, Tetraspan, Venofundin, Volulyte and Voluven.

News from the EU

Restrictions on the use of codeine for pain relief in children

The use of codeine for pain relief in children and adolescents under the age of 18 will now be restricted following an EU-wide safety review. The review was initiated based on reports of serious cases of opioid toxicity comprising, among other things, serious respiratory difficulty in children after taking medicines containing codeine for pain relief.

In Denmark, codeine is generally not used for pain relief in children.

The following recommendations apply to the use of codeine for pain relief in children:

- Codeine should only be used for the treatment of moderate pain in children aged 12 to 18 years that cannot be relieved by painkillers such as paracetamol or ibuprofen alone. Codeine should be used at the lowest effective dose for the shortest possible time.
- Codeine should not be used in children under 12 years of age due to the risk of opioid toxicity caused by the varying and unpredictable metabolism of codeine to morphine.
- Codeine should not be used in children with conditions where the respiration may already be affected, since the effect of codeine on the respiration may be enhanced in these cases.

Codeine is contraindicated in:

- All children aged 0 to 18 years undergoing tonsillectomy and/or adenoidectomy for obstructive sleep apnoea, due to a potentially increased risk of developing serious and life-threatening adverse reactions.
- All patients of any age who are known to be CYP2D6 ultra-rapid metabolisers.
- Women who are breastfeeding, because codeine and morphine can pass to the baby through breast milk.

Codeine is converted to morphine in the liver by the CYP2D6 enzyme. Variations in CYP2D6 may lead to lack of efficacy or insufficient efficacy (slow metabolisers, estimated to account for approx. 7% of the Caucasian population) or an increased risk of opioid toxicity due to higher morphine concentrations (ultra-rapid metabolisers, estimated to account for approx. 3.6-6.5% of the Caucasian population).

Some of the reports concerning serious adverse reactions in children turned out to be related to children who were CYP2D6 ultra-rapid metabolisers.

Read more about the review and the recommendations from the European Medicines Agency: *Restrictions on use of codeine for pain relief in children – CMDh endorses PRAC recommendation*

News from the EU

Risk of developing peripheral neuropathy during use of the fluoroquinolones class of antibiotics

The American Food and Drug Administration, FDA, recently issued an announcement concerning fluoroquinolones and the risk of developing peripheral neuropathy following oral and intravenous use. The FDA has required a review of the summaries of product characteristics, SPCs, for these drugs. The following must be specified in the SPCs: Peripheral neuropathy may occur soon after initiating these drugs and patients should be switched to another antibiotic treatment in case this adverse reaction occurs, unless the benefits of continued treatment with fluoroquinolones outweigh the risk of developing potentially permanent neuropathy.

In Denmark, the fluoroquinolones used for treatment are moxifloxacin (Avelox®) and ciprofloxacin (Cifin® etc.). Neuropathy is mentioned in the SPCs and package leaflets, PILs, for these drugs. See *www.produktresume.dk.* (in Danish only).

As a doctor you should be aware of the following:

- Patients treated with fluoroquinolones should be instructed to contact their doctor, if they develop symptoms of neuropathy, including pain, a burning sensation, pricking and tingling, numbness and/or weakness. The treatment should be discontinued, if the patient develops these symptoms, in order to prevent development of an irreversible condition.

It appears from the Danish Health and Medicines Authority's (DHMA's) guidelines for doctors on the use of fluoroquinolones that:

- Fluoroquinolones should only be used in case of microbiological diagnostics showing that other products are not applicable, or where the pharmacological properties of fluoroquinolones are particularly suited, and/or where the patient is allergic to penicillins.

See the guidelines on the DHMA's website: *Guidelines on Prescribing Antibiotics*

Report of urinary retention in association with the use of atomoxetine

In June 2013, the Danish Health and Medicines Authority received a report concerning a 16-year-old patient who developed urinary retention in association with the use of Strattera® for ADHD.

The patient had been treated with Strattera® over several periods of time. The last period spanned from November 2012 to May 2013, where the patient was admitted to a hospital with urinary retention. The patient's bladder was emptied and a catheter inserted therein. The catheter was removed a week later, but the following day the urinary retention recurred. The medicine was then discontinued. At the time of this report the patient still had urinary retention.

Nine reports of difficulty in micturition and urinary retention
The DHMA has received a total of nine reports of difficulty in micturition and urinary retention in association with the use of atomoxetine.

As a doctor you should be aware of the following:
The summary of product characteristics for Strattera® specifies that complaints about urinary retention or delayed micturition in adults should be considered to be potentially related to atomoxetine.

Indication for Strattera®
Strattera® is indicated for the treatment of ADHD in children of 6 years and older, in adolescents and in adults as part of a comprehensive treatment programme.

The Danish Health and Medicines Authority's report on NSAIDs – a study of the number of users, reported suspected adverse reactions and inadvertent incidents

In a report, the Danish Health and Medicines Authority (DHMA) has reviewed the number of users, reported suspected adverse reactions and inadvertent incidents for non-steroidal antiinflammatory drugs (NSAIDs).

NSAIDs are among the most commonly used drugs in Denmark. They are used as pain relieving, antiinflammatory and fever reducing agents. A Danish study has shown that, during a period of eight years, almost 60% of the adult Danish population redeemed one or more prescriptions for an NSAID product.

The DHMA's report reviews the status on knowledge of adverse reactions and consumption for NSAIDs with a particular focus on gastrointestinal adverse reactions and cardiovascular adverse reactions, since these adverse reactions in particular have been discussed repeatedly by both researchers and authorities.

Read the report here (in Danish only): *Sundhedsstyrelsens rapport om NSAID'er – forbruget, indberettede formodede bivirkninger og utilsigtede hændelser (The Danish Health and Medicines Authority's report on NSAIDs – the consumption, reported suspected adverse reactions and inadvertent incidents)*

All cases referred to in the articles in the Danish Pharmacovigilance Update originate from the Danish Health and Medicines Authority's adverse reaction database. 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.

Short news

Strong interest in Drug Analysis Prints with data from Danish adverse reaction reports

Since May last year, where the Danish Health and Medicines Authority (DHMA) made listings of information from Danish adverse reaction reports submitted by doctors, patients and their relatives, publicly available on the DHMA's website, the site has been popular with more than one thousand unique visitors.

Overview of the number of suspected adverse reactions reported

The listings are called Drug Analysis Prints (DAPs) and contain all the adverse reactions reported by active substance. Thus, the DAPs provide an opportunity to gain an overview of the suspected adverse reactions reported to the DHMA, and also of the development in the number of reports.

DAPs – a useful tool in everyday clinical practice

If you, as a doctor, suspect that a particular active substance may cause adverse reactions, the DAPs can be used to check for previous adverse reactions reported for the substance in question.

The DAPs may also help, e.g., scientists focus on safety issues which require further investigation.

The DAPs contain information about suspected adverse reactions, and it is therefore not certain that the adverse reactions were caused by the medicine listed.

The DAPs are in English and are anonymised printouts from the DHMA's adverse reaction database.

In the DAPs, the adverse reaction reports are grouped by System Organ Class. This means that, e.g., suspected adverse reactions related to mental disorders are grouped together.

The DAPs are updated monthly.

See the DAPs on the DHMA's website: *Drug Analysis Prints: Adverse reactions reported*

Short news

Prevention of cervical cancer

- Every year approx. 400 Danish women are diagnosed with cervical cancer.
- Every third day a woman dies in Denmark due to cervical cancer.
- Most cases of cervical cancer can be prevented. This can be accomplished by vaccinating girls at the age of 12 and by regular examination (screening) of women from the age of 23 years.

Prevention of cervical cancer

Cervical cancer is caused by Human Papillomavirus (HPV) which is passed on during sex. The vast majority of women will be infected with this virus at some point in their lives. Many women can combat these infections themselves, but some women cannot and develop a chronic infection with a risk of developing cervical cancer.

In 2007, the Danish Health and Medicines Authority (DHMA) prepared a comprehensive HTA report concerning HPV vaccination of women for the prevention of cervical cancer. The Danish recommendations and the offer of vaccination to girls at the age of 12 are based on this report and the clear scientific evidence in this field. The age of 12 was selected in order to vaccinate prior to the first sexual intercourse.

In the Danish immunisation programme, the vaccination is performed with the HPV vaccine Gardasil. This vaccine has been approved by the medicines regulatory agencies all over the world. In Europe, the vaccine has been approved by the European Medicines Agency EMA, of which Denmark is a member. In the USA, it has been approved by the FDA. The vaccine efficacy is highest when the vaccine is given prior to the first sexual intercourse, but most young sexually active women will benefit from being vaccinated.

Vaccine – effect and adverse reactions

There are many different types of HPV. Gardasil has a preventive effect after three vaccinations given within six months. This vaccine prevents infection with the HPV types 6, 11, 16 and 18. In approx. 70% of the cases, cervical cancer is caused by the latter two types.
No vaccine is 100% effective. Neither is Gardasil. Therefore, it is also important to participate in the screening from the age of 23 years.

All medicines can cause adverse reactions. It also applies to vaccines. A medicine is only approved, if the benefits of using it outweigh the risks.

The adverse reactions are studied in trials prior to approving a vaccine. Following approval and marketing of the vaccine, the monitoring of adverse reactions is continued, and the manufacturer keeps the product information updated with information on any newly identified adverse reactions. The product information specifies that Gardasil may cause adverse reactions such as swelling, redness and pain at the injection site, headache, nausea, pain in extremities and more rare adverse reactions such as fainting, convulsions, rash and the neurological disorder Guillain-Barré syndrome.

Danish authorities, European authorities, the WHO and the FDA and others are monitoring the occurrence of adverse reactions from the use of the vaccine – and an intervention will take place in case of a substantial negative shift in the benefit/risk balance.

Adverse reactions in Denmark are monitored closely

Adverse reactions from the use of vaccines, including HPV vaccination, are given special attention in Denmark. All serious suspected adverse reactions in Denmark are published on the DHMA's website to ensure openness and transparency. The website contains an overview of the occurrence of the various adverse reactions reported as well as the DHMA's assessment of the possibility of a correlation between the suspected adverse reactions and the vaccine. The DHMA will continue to publish this information. The next update is expected to be published in September 2013. In Denmark, at least 350,000 women have now been vaccinated. Worldwide, some 170 million doses have been distributed.

Until 26 August 2013, the DHMA had received a total of 786 adverse reaction reports, of which 129 were classified as serious. The serious adverse reactions most frequently reported are fainting/dizziness and anaphylaxis. The DHMA found no risk of cancer, and no fatal cases were reported.

The vast majority of the suspected adverse reactions reported are already described in the summary of product characteristics. However, during the summer, following news in the media concerning the HPV vaccine and adverse reactions, the DHMA has received an increased number of reports of adverse reactions classified as serious and adverse reactions that are not described in the product information. The adverse reactions reported to date have not given rise to a change in the safety profile for Gardasil, but the development is monitored closely.

The serious adverse reactions reported comprise a number of symptoms of various autoimmune and neurological diseases, but with no pattern. A uniform pattern among the adverse reaction reports would have been expected, if these symptoms had been caused by the vaccine. Whether or not the vaccine could cause such diseases >

> cannot be determined based on the individual reports. However, a major Nordic study not yet published rejects such a correlation. The study was conducted by the Statens Serum Institut, National Institute for Health Data and Disease Control, among others, and followed approx. 900,000 Swedish and Danish women, of whom approx. 300,000 have been HPV vaccinated. The study did not show an increased incidence of these diseases in the vaccinees. Even though this study rejects a correlation, and the reports do not indicate a correlation either, it continues to be important to monitor the adverse reactions from the vaccine closely.

The benefits of the vaccine outweigh the risks

In Denmark – as in the rest of Europe – the benefits and risks of the vaccine are assessed continuously. And the DHMA maintains its assessment that the benefits by far outweigh the risks, even though the vaccine, in very rare cases, may cause serious adverse reactions.

All adverse reactions are assessed by the EMA. Gardasil has been assessed four times during 2006 and 2007 and after that once annually. The benefits were determined to outweigh the risks in all assessments. The next assessment will be conducted at the end of 2013, and there are no signs that it will differ from the previous – and all positive – assessments. In the spring of 2013, the WHO completed its most recent assessment. Here too the benefits were assessed to outweigh the risks. Persons experiencing serious adverse reactions should contact their doctor to be diagnosed and started on a treatment.

The overall assessment is that the vaccine serves its purpose, i.e. to be an essential element in the prevention of cervical cancer. In rare cases, the vaccine may cause adverse reactions, and in very rare cases serious adverse reactions. However, in Denmark – as in the rest of Europe – the benefits of the vaccine are assessed to outweigh the risks by far.

HTA report on HPV vaccination (2007)

Product information on the HPV vaccine (Gardasil) (in Danish only)

WHO's assessment of HPV vaccines (2013)

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