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EMA tightens guidelines for use of hydroxyzine-containing medicines (Atarax®, etc.) to minimise the risk of heart rhythm disturbances

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recently concluded a considerable review of medicines containing the antihistamine hydroxyzine. The review was initiated because the medicine was suspected of increasing the risk of heart rhythm disturbances.

The PRAC established that hydroxyzine is associated with a small but definite risk of QT prolongation and consequently torsade de pointes.

PRAC's new recommendations for hydroxyzine:

- Hydroxyzine should be used at the lowest effective dose for as short a time as possible. The maximum daily dose should not exceed 100 mg in adults.
- Hydroxyzine is not recommended in the elderly. If use cannot be avoided in the elderly, the maximum dose should not exceed 50 mg.
- In children weighing less than 40 kg, the maximum dose should not exceed 2 mg per kg body weight.
- Use of hydroxyzine must be avoided in patients who already have risk factors for heart rhythm disturbances or are taking other medicines that increase the risk of QT prolongation.
- Hydroxyzine should be used cautiously in patients taking medicines that slow the heart rate or decrease the level of potassium in the blood as these medicines also increase the risk of heart rhythm disturbances.

In 2013, 7,659 people were treated with hydroxyzine in Denmark[1].

Indication for hydroxyzine
The hydroxyzine-containing medicines available in Europe are authorised for use in a number of indications, but the PRAC assesses that the risk of heart rhythm disturbances is unrelated to the indication.

In Denmark, hydroxyzine is authorised for symptomatic relief of anxiety in adults and management of symptomatic pruritus.

[1]Source: Medstat

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[1].

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

The most important safety signals discussed on the PRAC meeting in January 2015 concern the following products:

- **Statins** – Immune-mediated necrotizing myopathy (IMNM)
- **Gadodiamide, gadopentetic acid, gadoversetamide** – Nephrogenic systemic fibrosis in patients with acute kidney injury
- **Lithium** – Renal tumours
- **Paroxetine** – Aggression
- **Valproate and related substances** – Mitochondrial toxicity

See EU's list of recommendations on safety signals: *PRAC's recommendations on signals for updating of product information*

[1] The fact that a signal has been assessed does not mean that there is a causal link to the medicine.

Be aware of the risk of pulmonary fibrosis in long-term treatment with nitrofurantoin (Nitrofurantoin DAK) – new review and analysis by DHMA

More reported adverse reactions than expected

The DHMA has received an increasing number of ADR reports from doctors describing pulmonary fibrosis in connection with an older antibiotic nitrofurantoin for treatment of urinary tract infections. There are signs that the incidence of pulmonary fibrosis associated with nitrofurantoin treatment is higher in Denmark than described in the medicine's summary of product characteristics.

In response to this development, we have reviewed and analysed the reported adverse reactions and discussed the problem with ADR managers[1] in the Capital Region of Denmark and specialists from the Department of Clinical Microbiology at the Copenhagen University Hospital and the Department of Pulmonary Medicine at Gentofte Hospital.

Read the full review and analysis of nitrofurantoin and development of pulmonary fibrosis at the DHMA website:
Be aware of the risk of pulmonary fibrosis in long-term treatment with nitrofurantoin (in Danish only).

Advice for doctors

There is still inadequate evidence on long-term treatment with nitrofurantoin and the risk of pulmonary fibrosis, which is why it is important for doctors to recall that long-term treatment with nitrofurantoin could cause irreversible pulmonary fibrosis.

All patients receiving long-term treatment with nitrofurantoin should be screened for dyspnoea and dry cough, and the pulmonary function should be monitored. Nitrofurantoin should be discontinued at the first signs of changes:

- A pulmonary function test (spirometry) should be performed at the start of treatment and subsequently 3-4 times a year.
- Be aware that the symptoms may be absent until the disease is well-advanced and the changes in the lungs are irreversible.
- If changes in pulmonary function occur (≥ 10% fall in forced vital capacity (FVC)) or if there are clinical signs of reduced pulmonary function, nitrofurantoin should be stopped.

In the period 2004-2013, 229,635 persons redeemed one prescription or more for nitrofurantoin. In that period, we received 31 ADR reports that described the development of pulmonary fibrosis.

Indication for nitrofurantoin
Urinary tract infections caused by bacteria susceptible to nitrofurantoin.

[1]A regional ADR manager assists doctors with reporting suspected adverse reactions to the Danish Health and Medicines Authority. Presently, only the Capital Region of Denmark and Region Zealand have an ADR manager.

The number of melatonin users under 25 years of age keeps increasing

A recent report shows that more and more people younger than 25 years receive melatonin-containing medicines. Read more in the new report from the DHMA: *Development in the number of melatonin users younger than 25 years of age from 2007-2014 (in Danish only)*

Also see the DHMA's earlier reports of melatonin users younger than 25 years of age. *Melatonin users younger than 25 years of age (in Danish only).*

Development in the number of melatonin users younger than 25 years of age from 2007-2013 (in Danish only)

DHMA keeps watch on isotretinoin for acne treatment

A recommendation about isotretinoin in the Danish publication 'Rational Pharmacotherapy' from October 2014 may change the consumption pattern of isotretinoin-containing medicines, implying that more people will be treated with the medicine. In response, the DHMA will be keeping closer watch on isotretinoin's consumption pattern and reports of suspected adverse reactions related to isotretinoin products.

The publication 'Rational Pharmacotherapy' addresses acne therapy with the focus on antibiotic resistance and how to reduce antibiotic consumption. It is emphasised that systemic antibiotic treatment should be as short-termed as possible and combined with topical treatment. Furthermore, the authors recommend that isotretinoin treatment should be initiated earlier, possibly at low doses, which could save a lot of long-term antibiotic treatment courses.

Special awareness when treating women of child-bearing age

The recommendation may shift the consumption pattern so that more people are treated with isotretinoin, including women of child-bearing age. Isotretinoins have teratogenic effect and is therefore contraindicated in fertile women unless all precautionary measures described in the pregnancy prevention programme are followed.

Consequently, the DHMA will monitor the consumption pattern for isotretinoin with a special focus on women of child-bearing age.

Today, more women of child-bearing age use isotretinoin

Compared to two years ago, more women aged between 15-39 years use isotretinoin. In 2013[1], 1,083 women in this age group were issued one prescription or more for this medicine. This is an increase of 10% on the year before.

ADR reports on isotretinoin and teratogenic effect

The DHMA has received an ADR report that describes teratogenicity as a suspected adverse reaction to isotretinoin in a woman treated with isotretinoin gel during the first weeks of pregnancy. Foetal brain malformation was verified later in pregnancy.

In addition, we have received an ADR report on chromosome abnormality as a suspected adverse reaction to isotretinoin. A man fathered a child with a chromosome abnormality while he was being treated with isotretinoin. However, there is no knowledge that children of male patients taking isotretinoin will be affected (see below).

[1]Source: Medstat

Doctors should be aware of the following:

- Oral retinoids have been associated with congenital malformations.
- When topically administered isotretinoin is used in accordance with the recommended dose, there is negligible systemic absorption.
- However, the risk cannot be excluded since other factors may contribute to systemic exposure, e.g. the use of other products, skin barrier integrity, etc. Therefore, topical isotretinoin is not recommended during pregnancy or in women of child-bearing age who are not using an effective method of contraception.
- There are no indications that men's fertility or the children they have will be affected because of isotretinoin use. However, male patients should be reminded not to share their medicine with others, especially not women.

We also refer to the pregnancy prevention programme in the summary of product characteristics of isotretinoin.

Indications for isotretinoin
Severe forms of acne (such as nodular or conglobate acne or acne at risk of permanent scarring), resistant to adequate courses of standard therapy with systemic antibacterials and topical therapy.

DHMA has focus on ADHD medicines and cardiovascular disturbances

The DHMA is watching medicines for treatment of ADHD – including methylphenidate. Over the past four years, we have received three ADR reports of fatal outcomes in connection with methylphenidate treatment. All three reports describe antecedent cardiovascular disturbances. In addition, we have received one report about a boy who, while being treated with Concerta®, went into cardiac arrest from which he suffered permanent injuries. He survived, but a pacemaker was implanted. The boy was later awarded compensation from the Danish Patient Compensation Association.

Because of these events the DHMA once again directs its attention to ADHD medicines and possible adverse reactions, focusing especially on possible cardiovascular effects.

Previous focus on ADHD medicines

The DHMA has previously kept a vigilant eye on ADHD medicines. See more on the DHMA website and in Danish Pharmacovigilance Update: *www.dhma.dk*

Tramadol (Mandolgin®, etc.) and convulsions

In January, the DHMA received a report about a patient who received Mandolgin® for hip pain.

The patient suffered two tonic-clonic seizures after having taken the medicine, the first one occurring eight hours after intake, the last one approx. 12 hours after intake. The medicine was discontinued, and the patient did not have seizures again.

Ten months earlier, the patient was given the medicine in connection with hip surgery and did not have any seizures, but eight years earlier the patient had suffered a seizure with no link to a medicine. The patient had not been examined for epilepsy.

The DHMA has received altogether 16 ADR reports that describe patients suffering convulsions, spasms or epileptic seizures as suspected adverse reactions to tramadol.

Doctors should be aware of the following:

- There have been reports of convulsions in patients treated with tramadol within the recommended dosing interval. The risk may increase if the tramadol dose exceeds the recommended upper limit of 400 mg daily.
- Tramadol may also increase the risk of convulsions in patients who concurrently take other medicines that lower the seizure threshold (e.g. MAO inhibitors, tricyclic antidepressants and selective serotonin reuptake inhibitors).
- Patients who have a history of epilepsy or other risk factors for seizures should only be treated with Mandolgin® if there are compelling reasons.

Indication for tramadol
Moderate to severe pain.

Pay attention to patient's renal function before and during treatment with the non-vitamin K antagonists Pradaxa®, Eliquis and Xarelto®

In January 2015, the DHMA received an ADR report about an 85-year-old patient with known nephropathy. The patient had been treated with the non-vitamin K antagonist Marevan® for several years, but in autumn 2014 the patient was switched to Xarelto® and later Pradaxa® 110 mg twice daily to treat the indication of atrial fibrillation. The patient was prescribed Pradaxa® several times, including from a Department of Nephrology in October 2014.

At end-April 2014, a test showed that the patient's creatinine clearance (CrCl) was 16 ml/min.

In January 2015, the patient was admitted to hospital with respiratory distress. There were indications of organ failure (liver effects, reduced pump function and anuria). The patient was bleeding from injection sites, APTT was considerably increased, and thromboelastography showed zero coagulation. In addition, the risk of bleeding made it impossible to insert a dialysis catheter or to perform surgery. The patient died within the first 24 hours of hospitalisation.

Pradaxa®, Xarelto® and Eliquis are contraindicated in patients with severe renal impairment

Doctors should be aware that these medicines are contraindicated in patients with severe renal impairment and that the thresholds vary between the three non-vitamin K antagonists (NOACs)

- Pradaxa® is contraindicated in patients with severe renal impairment CrCl< 30 ml/min.
- Xarelto® and Eliquis are contraindicated in patients with CrCl <15 ml/min.

Renal function should always be measured prior to initiation of either of the three NOAC products.

Recommendations from the Danish Society of Cardiology.

The Danish Society of Cardiology recommends that all patients have their renal function tested every three months in the first year, and thereafter according to individual evaluation based on the course of events, renal function, comorbidity and other medication. Renal function should be assessed by calculating/evaluating creatinine clearance.

In addition, the renal function should be assessed in special clinical situations whenever a decline in renal function is suspected. In elderly patients, clinical situations could develop such as gastroenteritis with vomiting and/or diarrhoea leading to dehydration, which again could lead to a decline in renal function and thus higher concentrations of anticoagulant in the blood. In such scenarios, the renal function must be monitored and the anticoagulant dose reduced as needed to avoid severe bleeding.

Read more on the website of the Danish Society of Cardiology *Oral anticoagulant treatment with vitamin K antagonists (in Danish only).*

Increased focus on safety when NOAC products are used in treatment

The DHMA has maintained a continuous increased focus on safety related to treatment with the three new oral anticoagulants (NOACs). This recent report and new data from the Thrombosis Research Unit, Aalborg Hospital, prompt us to make doctors aware that it is extremely important to monitor the renal function when these medicines are used.

New data from the Thrombosis Research Unit, Aalborg Hospital, on NOAC therapy and patients with renal disease

Fresh data from the Thrombosis Research Unit, Aalborg Hospital, clearly show that doctors take account of the renal function when choosing between Xarelto® or Pradaxa® for patients with atrial fibrillation who are to receive anticoagulant treatment for the first time. The proportion of patients with a kidney disease (diagnosed before treatment initiation) who

[1]Source: Danish National Patient Registry

start on Xarelto® is larger than for Pradaxa®. In the period February 2012 to August 2014, 1.1 % of patients registered with a renal disease (60 patients) started treatment with Pradaxa® 150 mg and 2.5 % (88 patients) started treatment with Pradaxa® 110 mg. For Xarelto®, there were 1.5% (25 patients) who started on 20 mg and 10.1 % (78 patients) who started on 15 mg[1].

It should be noted that it is not possible to extract data about the patients' creatinine clearance from the national health registers, and therefore we do not know the degree of renal function impairment for the kidney diseases registered in the Danish National Patient Registry. Nonetheless, it is potentially worrying that 10.1 % of the users taking Xarelto® 15 mg are registered with a kidney disease against the 6.5 % who are started on warfarin considering that warfarin can be used in patients regardless of renal function capacity.

Read more on the website of the Danish Society of Cardiology *Anticoagulant treatment (in Danish only)*

Previous announcements about NOACs

Since the NOACs were marketed, the DHMA and the Danish National Agency for Patients' Rights and Complaints have regularly sent out announcements with descriptions of reported cases with bleeding complication outcomes due to non-compliance with the summaries of product characteristics.

Read the other announcements:

Patients with mechanical heart valves not to be treated with new oral anticoagulants – in Danish only.
DHMA issues warning about blood thinners – in Danish only
Bulletins from the Danish National Agency for Patients' Rights and Complaints (in Danish only)

[1]Source: Danish National Patient Registry

Short news

Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been (or soon will be) sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- **The glucocorticoids Solu-Medrol (methylprednisolone sodium succinate) and Solu-Cortef (hydrocortisone sodium succinate):** Solu-Medrol and Solu-Cortef should be used immediately after reconstitution

The DHPCs are available in Danish at the DHMA website: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals.*

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