Danish Pharmacovigilance Update Year 3 #10
15 November 2012

Chlorhexidine and the risk of anaphylactic reaction

The Danish Health and Medicines Authority urges doctors to be aware that, in rare cases, chlorhexidine may trigger an anaphylactic reaction. A number of drugs (including OTC drugs) and medical devices contain chlorhexidine. Examples of product types that may contain chlorhexidine are antiseptic creams/gels, wipes and cleansers; antiseptic mouthwashes and dental implants; eye drops and contact lens solutions; antiseptic lozenges and throat sprays; urinary catheters; central venous catheters; and antiseptic dressings.

The Danish adverse drug reaction database contains a total of seven reports of anaphylactic reaction following the use of medicinal products containing chlorhexidine. This risk is addressed in a number of references in the international literature.

As a doctor you should be aware of the following:

- ensure that known allergies are recorded in patient records.
- check the summary of product characteristics and instructions for use to establish whether a product contains chlorhexidine prior to use in patients with a known allergy.
- if a patient experiences an unexplained reaction, check whether the reaction followed the use of a product containing chlorhexidine.
- report allergic reactions to products containing chlorhexidine to the Danish Health and Medicines Authority: *drug medical device*

All cases referred to in the article 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.

Consumption and safety of cholesterol-lowering medicines

In recent years, the consumption of statins has increased, and they now rank among the largest-selling drugs in Denmark.

The Danish Health and Medicines Authority has made a review of Danish reports showing that the number of adverse reactions reported in association with statins has increased with the number of users. In some cases, the adverse reactions are serious, but well-known and described in the product information.

As part of our conclusion, we recommend the following to help ensure appropriate and safe use of statins:

As a doctor you should be aware of the following:

- You should only consider prescribing statins in high doses to high-risk patients. High-risk patients are patients with e.g. very high levels of cholesterol and a history of heart attack or patients with severe type 2 diabetes. The risk of serious muscular adverse reactions, the main concern associated with the use of statins, is dose-dependent, and data from the Danish Register of Medicinal Product Statistics (SSI) have shown that more and more patients are prescribed the highest dose.
- Regardless of the dose of statins a patient is given, as a doctor you should be aware of the risk of interactions with other medicines. In case of interactions, the patient should stop taking other medicines, or the dose of statins should be reduced. Analysis of the adverse reactions reported concerning serious muscular adverse reactions has shown that the patients had often also received other medicines known to affect the treatment with statins and to increase the risk of muscular adverse reactions in general.
- You should balance the expected benefits of the statins with the risk of adverse reactions for each patient prior to initiating treatment – especially in case of primary prophylaxis.

Read the Danish Health and Medicines Authority's focus report *Fokusrapport – Viden om forbrug og bivirkninger ved behandling med statiner (Focus report – Knowledge of consumption and adverse reactions from the use of statins, in Danish only).*

Benefits of NSAIDs continue to outweigh the potential risk of cardiovascular adverse reactions – however, the risk associated with diclofenac requires further investigation

The European Medicines Agency, EMA, has finalised a review of the most recent data on cardiovascular adverse reactions from the use of painkillers of the NSAID type. The conclusion is now available and confirms findings from previous reviews, conducted in 2005 and 2006, namely that the benefits of NSAIDs continue to outweigh the risks.

The main focus of the review was the most widely used NSAIDs: ibuprofen, naproxen and diclofenac.

For ibuprofen and naproxen, the Agency finds that the current product information is adequate. For diclofenac, the most recent evidence indicates that the risk of cardiovascular adverse reactions is slightly increased. The risk is similar to the risks of COX-2 inhibitors.

The European Pharmacovigilance Risk Assessment Committee, PRAC, will now assess the data on diclofenac

As a follow-on to this review, the European Pharmacovigilance Risk Assessment Committee, PRAC, has now initiated an assessment of all available data on diclofenac to investigate the need for updated treatment advice for this NSAID type.

Read also EMA's press release. *European Medicines Agency finalises review of recent published data on cardiovascular safety of NSAIDs*.

You can find further information on *the Danish Health and Medicines Authority's website*.

The European Medicines Agency, EMA, is reviewing data on medicines containing codeine, especially concerning the use in children

On 3 October 2012, the European Medicines Agency, EMA, started a review of medicines containing codeine.

The reason for this review is a recently increased incidence in EU countries other than Denmark of morphine intoxication in children who were given codeine after surgical removal of the tonsils or adenoids. A small number of life-threatening and a very small number of fatal cases have been reported of respiratory depression in children.

The EMA will evaluate the impact of this information on the benefit-risk balance of medicines containing codeine when used for pain relief in children.
Read more on *the Danish Health and Medicines Authority's website*, where you can also find a link to the announcement from the EMA.

Indication for medicines containing codeine

Used as analgesics for mild to moderate pain. In Denmark, medicines containing codeine are not approved for use in children under 15 years of age and neither for pain relief after surgical removal of the tonsils or adenoids.

Renal impairment in association with the use of ciclosporin (Sandimmun Neoral® and others)

In the summary of product characteristics for ciclosporin, renal impairment is described as a very common and well-known adverse reaction. During the first few weeks of treatment with ciclosporin, increase in serum creatinine and urea is a frequent and potentially serious complication. These functional changes are dose-dependent and reversible and will respond to dose reduction.

The Danish Health and Medicines Authority has received a total of 26 reports of patients who developed renal impairment in association with the use of ciclosporin. For eight of these reports, the indication was prevention of graft-versus-host disease in association with transplants. Of these, five were associated with kidney transplants.

In September 2012, the Authority received an adverse reaction report concerning a patient treated with the product Sandimmun Neoral® in association with a bone marrow transplant. The patient developed irreversible renal impairment.

These reports occasion us to remind you, as a doctor, to be particularly aware of the following as regards ciclosporin:

- Ciclosporin is contraindicated in patients with renal impairment, except for patients with nephrotic syndrome and mild to moderate renal insufficiency.
- Close monitoring of parameters that assess the renal and hepatic function is required. Abnormal values may necessitate dose reduction.
- During long-term treatment, some patients may develop structural changes in the kidneys (e.g. interstitial fibrosis) which, in kidney transplant patients, may be confused with changes due to chronic rejection.
- Care should be exercised when using ciclosporin together with other drugs which by themselves may cause renal impairment such as aminoglycosides, non-steroidal anti-inflammatory drugs, histamine H2-receptor antagonists, methotrexate and sirolimus.

Indication for Sandimmun Neoral®

– Prevention and treatment of graft-versus-host disease in association with organ transplants.
– Sight-threatening intermediate and posterior uveitis and Behcet's uveitis.
– Nephrotic syndrome.
– Severe rheumatoid arthritis.
– Severe psoriasis.
– Severe treatment-refractory atopic dermatitis.

Persons initiated on treatment with Champix® (varenicline) for smoking cessation should be prescribed the recommended starter pack containing starting doses

The Danish Health and Medicines Authority has been informed that not all persons initiated on treatment with Champix® (varenicline) for smoking cessation are prescribed the recommended starter pack.

Using the starter pack ensures slow titration of the medicine, whereby the patient is slowly adjusted to the treatment, reducing the risk of adverse reactions.

As a doctor you should be aware of the following:

- You should always prescribe the starter pack to persons initiated on treatment with Champix® (varenicline).
- The maintenance dose is 1 mg of varenicline twice daily after 1 week of dose titration according to the following scheme:

Starting dose	Day 1 – 3	0.5 mg once daily
Starting dose	Day 4 – 7	0.5 mg twice daily
Maintenance dose	Day 8 – the rest of the treatment	1 mg twice daily

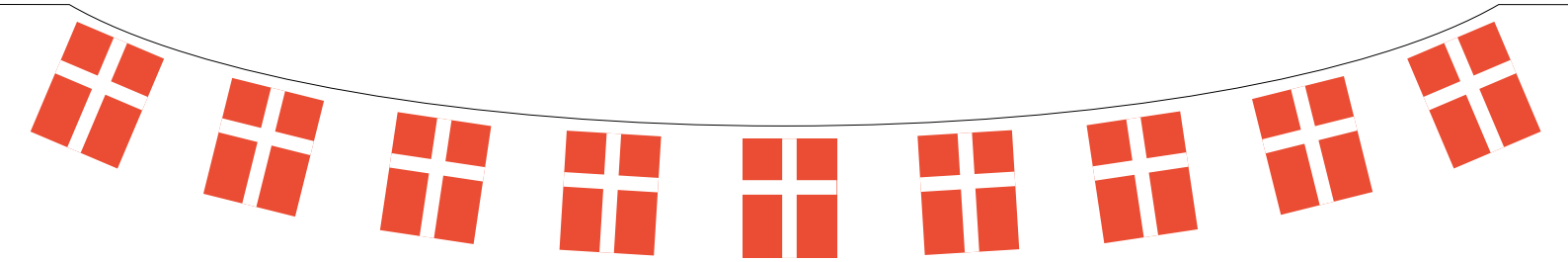
The Danish Health and Medicines Authority maintains influenza vaccine recommendation

The European Medicines Agency, EMA, has reviewed a hypothesis on Pandemrix® and the development of sleep attacks (narcolepsy). Overall, EMA assesses that there are no grounds for concerns regarding Pandemrix® and other vaccines, including influenza vaccines.

On this basis, the Danish Health and Medicines Authority maintains its influenza vaccine recommendation.

Read more on our *website*.

Danish Pharmacovigilance Update celebrates its 3rd anniversary



On 9 November 2009, the first issue of Danish Pharmacovigilance Update was released, which means that this year we are celebrating the 3rd anniversary of the newsletter with our approx. 2,200 subscribers.

The past three years has seen many different articles, ranging from updates of summaries of product characteristics and newly initiated studies to articles on withdrawals and cases of new serious adverse reactions.

In 2012, we have, e.g., published articles on the frequency of malformations in newborns after treating the mother with antidepressants (SSRI) during pregnancy *Danish Pharmacovigilance Update, March 2012*, on decrease in the number of intoxications and suicide attempts using drugs containing acetylsalicylic acid or paracetamol in *Danish Pharmacovigilance Update, June 2012* and on a new definition of adverse reactions due to new European legislation on pharmacovigilance in *Danish Pharmacovigilance Update, September 2012*.

We are very pleased about the strong interest and the positive response to the newsletter, and we hope the interest will continue to grow.

Subscribe to *Danish Pharmacovigilance Update* and see all previous issues of the newsletter *here*.

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