Danish Pharmacovigilance Update

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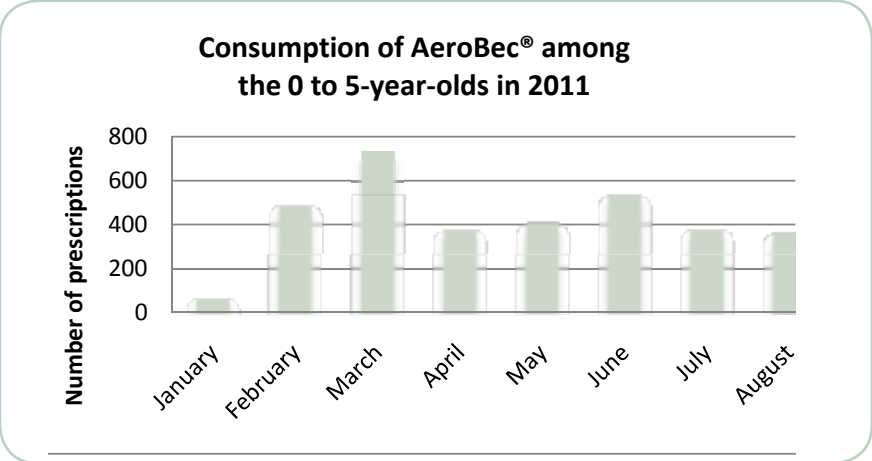
Significant increase in off-label use of AeroBec® in children under the age of five

The Danish Medicines Agency has become aware of a significant consumption of AeroBec® among children under the age of five – see chart. AeroBec® is only authorised for the prevention of asthma in adults and children over the age of five, and we do not know the effect and risks of AeroBec® when used in children younger than five.



It is possible that it is used off-label because AeroBec® fits the spacer used with Spirocort®, which was authorised for use in children younger than five, but whose production ceased in February 2011.

Authorised asthma medicine for children younger than five
Presently, there is only one spray on the market, Flixotide®, which is authorised in Denmark for use in small children. Flixotide® is authorised for children as young as 12 months.

Inquiry about article in Danish Pharmacovigilance Update from January 2011 on fluoroquinolones and risk of QT prolongation

The Danish Medicines Agency has been contacted in response to an article brought in the January 2011 issue about "Fluoroquinolones and risk of QT prolongation". The inquiry concerns ciprofloxacin's risk of QT prolongation. We were contacted because ciprofloxacin was not mentioned in the article.

The article from January summarised an investigation launched by the European Pharmacovigilance Working Party, PhVWP, on fluoroquinolones' risk of QT prolongation. At the time, ciprofloxacin-containing products were not covered by this investigation.

As mentioned in the January issue, the investigation concluded that fluoroquinolones can be divided into three groups based on their potential for inducing QT prolongation.

Ciprofloxacin's risk of QT prolongation
Since then, the PhVWP has looked at those products that were not included in the investigation – of which only ciprofloxacin-containing products are authorised in Denmark – and has divided them into the three groups based on already available knowledge. Ciprofloxacin was found to belong to the group of fluoroquinolones with a low potential risk of inducing QT interval prolongation - but ciprofloxacin should be used cautiously in patients with known risk factors for QT prolongation.

Read the article *"Fluoroquinolones and risk of QT prolongation"* in Danish Pharmacovigilance Update from January 2011, page 2.

NSAIDs and possible risk of cardiac adverse reactions

The Danish Medicines Agency has previously issued warnings about the use of medicines of the NSAID type. NSAIDs are primarily used to treat mild pain, arthritis and back pain and in migraine therapy. Now, new knowledge has emerged about a possible risk of cardiac adverse reactions from NSAID use.

New study suggests risk of heart attack

In May 2011, a Danish team of researchers published a registry study in *Circulation*, shedding light on the link between the duration of NSAID treatment, e.g. ibuprofen and diclofenac, and the risk of suffering a new heart attack in patients who had previously had a heart attack.

The main conclusion of the study was that NSAIDs are associated with this risk of heart attack, regardless of the duration of treatment. For some of the NSAIDs included in the study, an increased risk of a new heart attack was even seen already from start of treatment.

New study suggests risk of atrial fibrillation

In July 2011, another Danish group of researchers published a new registry study in BMJ, highlighting the risk of atrial fibrillation from the use of non-selective NSAIDs and selective cyclo-oxygenase (COX-2) inhibitors.

The main conclusion of this study was that non-selective NSAIDs (excluding acetylsalicylic acid) and COX-2 inhibitors seemed to be associated with a small increased risk of atrial fibrillation. The study identified seven extra cases of atrial fibrillation per 1000 new users of NSAIDs per year. There were most cases of atrial fibrillation among users of COX-2 inhibitors.

Knowledge already described in the SPC of NSAIDs

NSAID treatment is contraindicated in patients with severe cardiac failure, which is described in the applicable summary of product characteristics (SPC) for all NSAIDs. It is indicated clearly in the SPCs for NSAIDs that the lowest effective dose for the shortest duration necessary should be used to minimise the risk of undesirable effects. The following warnings are also included:

- A small increased risk of arterial thrombotic events have been observed.
- Patients with uncontrolled cardiovascular disease should only be treated with NSAIDs after careful consideration.
- Longer-term treatment of patients with risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes, and smoking) should only take place after careful consideration.

Assessment of potential need to update the NSAID SPC

The Danish Medicines Agency will bring up the case in the European Pharmacovigilance Working Party in September 2011 for an assessment of whether the product information needs to be clarified with respect to the duration of treatment and with respect to the possible risk of atrial fibrillation or flutter.

Warning against the product Melanotan (the Barbie drug)

The Danish Medicines Agency has received a number of inquiries and several adverse reaction reports on the product Melanotan. Melanotan is neither tested through nor authorised in Denmark, Europe or the USA, but it can be bought illegally on the internet.

We advise doctors to pay attention to patients in their care who inquire about the use or side effects of Melanotan.

Adverse reactions include fatigue, nausea, headache, reduced appetite, psychiatric symptoms, increased sex drive and development of moles. Using the substance could also increase the risk of developing cancer in pigment cells.

The Danish Medicines Agency has previously issued warnings on the use of Melanotan in August 2008 and again in June 2011. See the Agency's website: *Warning against the tanning product Melanotan*.

Melanotan, also nicknamed the Barbie drug, refers to two variants of the same synthetic peptide hormone (melanocortin): Melanotan I and Melanotan II. The products are used to achieve tanning without exposure to the sun.

The Danish Medicines Agency wants to receive reports of suspected antibiotic resistance

By international measures, Denmark has a relatively low consumption of antibiotics and a relatively low development of antibiotic resistance, but antibiotic consumption and resistance problems are growing nonetheless.

To tackle this development, the Danish Ministry of the Interior and Health together with the Danish Ministry of Food, Agriculture and Fisheries therefore joined forces to devise a common antibiotic and resistance action plan in May 2010.

In this connection, the Danish Medicines Agency has searched the adverse reaction database for reports of resistance. The database of adverse reactions contains very few reports of resistance and antibiotics. The low number of reports could be because antibiotic resistance is not a side effect, but it could also be because it is only the severe cases that are reported and that severe cases do not occur frequently.

We ask healthcare professionals to report cases of antibiotic resistance

In order to assess the scale of the problem, the Danish Medicines Agency would appreciate receiving reports of cases of antibiotic resistance. We therefore encourage healthcare professionals to report cases of development of resistance, i.e. cases of antibiotic treatment that had no effect.

The Danish Medicines Agency focuses attention on consumption and safety of biological medicines for children and adolescents

Biological medicines make up a new group of medicines which, throughout a decade, have delivered path-breaking improvements for the treatment of inflammatory diseases such as rheumatoid arthritis, Crohn's disease and severe psoriasis.

In recent years, more biological medicines have been approved for the treatment of children.

New medicines always need to be monitored closely to ensure proper use and to gather knowledge about adverse reactions. Biological medicines are almost only used in hospitals, and here, the Danish Medicines Agency cannot monitor consumption to the same extent as it can in the primary sector.

About half of the biological medicines used in Denmark are used in rheumatology.

Non-registration of children receiving biological medicines

DANBIO, a clinical quality registry in Denmark, registers data on the use of adverse reactions of biological medicines in adult rheumatology patients, but does not include the use of biological medicines in children. There are other registries in Denmark that register patients treated with biological medicines: Dermbio (dermatology patients) and DCCB (Colitis and Crohn's disease patients). These registers include children, but do not systematically record all children in treatment. In addition, the Danish Medicines Agency's database of adverse reactions only contain a few reports of children having experienced adverse reactions from the use of biological medicines.

The Danish Medicines Agency has therefore chosen to look closer at how biological medicines are used in children, and what the experiences are with effects and side effects of biological medicines. The analysis will be based on interviews with specialists, patients and relatives in Denmark compared against data from the Danish Medicines Agency's adverse reaction database, international studies and the drug regulatory authorities' knowledge from the licensing of medicines.

Danish Drug Interaction Database expanded with information about class effect, SAD products and product names for natural remedies and strong vitamins

An improvement has been made to the Danish website interaktionsdatabasen.dk, where doctors and healthcare professionals can find information about interactions between various medicines. The Drug Interaction Database has a Danish interface only.

It is now possible to search for:

- class effect – a general overview of how two different categories of medicinal product groups interact
- hospital pharmacies' SAD products
- active substance and product names for natural remedies and strong vitamins.

The new features of the Drug Interaction Database were launched based on requests from healthcare professionals and have to some extent also been implemented in the lighter version for consumers, at the Danish website medicinkombination.dk.

General overview of how two different categories of medicinal product groups interact (class effect)

Before, the Danish Drug Interaction Database did not include search results for interactions described in the scientific literature. For example, the interaction between enalapril and naproxen is not described in the literature, but the Drug Interaction Database now provides a general description of how the medicinal product groups interact, which may point to a potential interaction between the specific medicine combinations.

A new link has been inserted, which makes it possible to see a list of studies on interactions between medicines belonging to different groups of substances - in the example of enalapril and naproxen, the class effect between the groups ACE inhibitors and NSAIDs. The link also gives access to reading descriptions of interactions between other medicines of these groups.

Hospital medicines now also included

Medicines from hospital pharmacies in Denmark labelled "SAD" are also included in the Drug Interaction Database. One example is the strong vitamin thiamine, which is sold under many different product names. Thiamine is now also included in the Drug Interaction Database precisely as it is written by the hospital pharmacies, namely "Tiamin SAD".

Easier to search for interactions between natural remedies

Finally, information about herbal remedies has been fully integrated into the Drug Interaction Database, so instead of only being able to search on a herbal remedy's active substance, searching on the product's actual brand name is also possible.

It is a relevant improvement, because some herbal remedies go by different names, for example St. John's Wort, which is also known as hypericum and hypericum perforatum. With this change in the Drug Interaction Database, you can just search directly on, say, Modigen, which is one of the brand names for hypericum, and see how it interacts with other medicines. It could very well be relevant to check how herbal remedies interact with other medicines. This holds true for hypericum whose effect can actually make contraceptive pills ineffective.

See *www.interaktionsdatabasen.dk*

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