Danish Pharmacovigilance Update

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Maternal use of mild analgesics and risk of cryptorchidism

Two new Danish studies[1,2] suggest that consumption during pregnancy of mild over-the-counter analgesics, including paracetamol, may result in an increased risk of giving birth to baby boys with cryptorchidism (retentio testis).

The most extensive study[1] included 47,400 newborn Danish boys in the period from 1996 to 2002. Both during and after pregnancy, the mothers were asked about their consumption of analgesics during pregnancy.

The study showed that:

- Intake of paracetamol during both the first and second trimesters was associated with an increased occurrence of cryptorchidism – hazard ratio (HR) 1.33 (95 % confidence interval = 1.00-1.77) (dose not stated).

- Intake of paracetamol for more than four weeks within gestational weeks 8 to 14 was associated with a HR of 1.38 (1.05-1.83) for cryptorchidism (dose not stated).

Moderately increased risk

It is, however, important to emphasise that the increased risk is very moderate. Cryptorchidism is found in 2 to 3 percent of baby boys, and a HR of 1.33 is thus a very small increase in the absolute risk. In addition, the increased risk is only seen in women who have used paracetamol for a relatively long period of time (over 4 weeks).

Danish/Finish study

In the second study[2], 2297 Danish and Finnish pregnant women were interviewed about their use of mild analgesics during pregnancy. The Danish birth cohort showed that use of mild analgesics has a slight association with cryptorchidism. The association was not found in the Finnish birth cohort.

In addition, it cannot be ruled out that in these studies, other factors (diseases, consumption of stimulants, life style, etc.) could explain the findings.

Doctors must inform their pregnant patients that:

- they should always follow the general recommendations for using medicines during pregnancy: Take as little medicine as possible during pregnancy, which also includes over-the-counter medicines.

The summary of product characteristics states whether the medicine can or cannot be used during pregnancy. Danish summaries of product characteristics are available at the Danish Medicines Agency's website: *www.produktresume.dk*

In summary, it is the opinion of the Danish Medicines Agency that the association between analgesics and pregnancy must be examined more closely before it can be established if there is reason to change the general recommendations for use of analgesics during pregnancy.

Consequently, the Danish Medicines Agency has brought up the case in the European Pharmacovigilance Working Party to initiate a thorough examination and reassessment of the safety of paracetamol and other mild analgesics in pregnant women.

1 Maternal Use of Acetaminophen, Ibuprofen and Acetylsalicylic Acid During Pregnancy and Risk of Cryptorchidism, Jensen M.S. et. al., Epidemiology 2010; Volume 21, pp. 779-85.

2 Intrauterine exposure to mild analgesics is a risk factor for development of male reproductive disorders in human and rat, Kristensen D.M. et. al., Human Reproduction, 2010, pp. 1-10.

Oral bisphosphonates – not enough evidence for a causal relationship with oesophageal cancer

Based on a new study suggesting an increased risk of oesophageal cancer following treatment with bisphosphonates, the European Pharmacovigilance Working Party (PhVWP) has examined the evidence of this possible risk. The PhVWP has concluded that based on the current data, there is not enough evidence for a causal relationship between oral bisphosphonates and an increased risk of oesophageal cancer.

Doctors should be aware that:

- Bisphosphonates can cause oesophageal irritation, and therefore, it is still important to instruct patients to use the medicine according to directions and to contact the doctor if they experience any sign of oesophageal irritation.
- Patients with Barrett's oesophagus should only be treated with alendronate (Fosamax etc.) or ibandronate (Bondronat etc.) after thorough assessment of benefits compared to the possible risks of oesophageal irritation and exacerbation of the underlying disease.

Read PhVWP's monthly report: *here*

In Denmark, bisphosphonates are used increasingly in patients with osteoporosis. The Danish Medicines Agency are, at present, keeping a sharp eye on medicines containing bisphosphonates, and especially on the medicines' possible long-term adverse reactions.

Fibrates should be used only as a second-line treatment of hyperlipedemia

The European Committee for Medicinal Products for Human Use (CHMP) has in a recently completed report about fibrates (bezafibrate, ciprofibrate, fenofibrate, gemfibrozil) concluded that their benefits continue to outweigh their risks in treatment of patients with blood lipid disorders.

However, fibrates are recommended as a second-line treatment in newly diagnosed patients with blood lipid disorders and should be used only as first-line treatment in patients with severe hypertriglyceridaemia and in patients who cannot take statins.

Read CHMP's monthly report *here*

Out of the four fibrates included in the study, gemfibrozil (Lopid) is the only authorised fibrate on the Danish market.

Please report lack of antibiotic efficacy

Lack of efficacy of antibiotics due to antibiotic resistance is not an adverse reaction that doctors must report to the Danish Medicines Agency according to provisions regarding the reporting of adverse reactions. However, it is vital information because, in many situations, the right treatment with antibiotics can be crucial for the protection of patients' health.

Consequently, the Danish Medicines Agency urgently requests that doctors and other healthcare professionals report any lack of efficacy due to suspected antibiotic resistance.

Doctors and other healthcare professionals can report lack of efficacy on the same form they use to report adverse reactions. Find the Danish reporting form at *www.meldenbivirkning.dk* and the English form *here.*

Reports regarding lack of antibiotic efficacy are part of the Danish Medicines Agency's and the manufacturer's continuous market surveillance, and of the evaluation of the medicine's benefits and risks. In some cases, the Danish Medicines Agency can change, suspend or withdraw a marketing authorisation for medicine if the medicine's benefit-risk ratio becomes unfavourable.

Information on lack of efficacy might also be included in the guideline of the National Board of Health on use of antibiotics and prevention of antibiotic resistance.

For information, a Danish national antibiotic and resistance action plan has been adopted (in Danish only. Find the action plan *here*.

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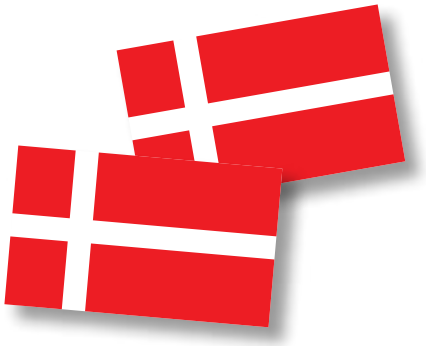

Danish Pharmacovigilance Update celebrates 1-year anniversary

The first issue of Danish Pharmacovigilance Update was published for the first time in November 2009. Today, the newsletter, primarily targeted doctors, has over 1400 subscribers, and new subscribers join constantly.

In total, we have published 11 issues during the newsletter's first year with articles on everything from updates on summaries of product characteristics, to medicines withdrawn from the market.

In the Danish Medicines Agency we are pleased with the great interest in the newsletter and not least in the pharmacovigilance area which is an important focus area.

In order to ensure that the newsletter's content is always scientifically relevant and always lives up to your expectations, we have on the occasion of Danish Pharmacovigilance Update's 1-year anniversary asked for your opinion of the newsletter (only in Danish).

Great satisfaction with the newsletter

In connection with the latest Danish issue of Danish Pharmacovigilance Update (26 October 2010) we sent out a Danish questionnaire to all our subscribers. In the questionnaire, we requested your opinion of the newsletter regarding both content, presentation and relevance. The answers to the questionnaire have formed the basis for an evaluation.

The survey showed that the newsletter is very satisfactory and that all the articles are read and seem relevant in proportion to practice.

We have also received many good suggestions for articles and themes which we will look at more closely with the Council for Adverse Drug Reactions.

Thank you for all the answers and the useful input to improve the newsletter.

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