Danish Pharmacovigilance Update

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Serious accidental overdoses of intravenous paracetamol (Perfalgan®)[1] in infants

A number of dosing errors involving Perfalgan® have been recorded.

Overdosing occurred because of confusion between 'mg' (the dose of paracetamol) and 'ml' (the volume of paracetamol solution for infusion), resulting in the administration of a dose 10 times higher than prescribed – the strength of Perfalgan being 10mg/ml.

Doctors should pay special attention to the dose for children and infants:

- **Children weighing more than 10kg (approx. 1 year old) and weighing less than 33kg:**
  Paracetamol 15mg/kg per administration, i.e. 1.5ml solution per kg up to four times a day. The minimum interval between each administration must be 4 hours. The maximum daily dose must not exceed 60mg/kg (without exceeding 2g).
- **Term newborn infants, infants, toddlers and children weighing less than 10kg (up to approx. 1 year old):**
  Paracetamol 7.5mg/kg per administration i.e. 0.75ml solution per kg up to four times a day. The minimum interval between each administration must be 4 hours. The maximum daily dose must not exceed 30mg/kg.
- ***Only* a very small volume may be administered to infants.**

The Danish SPC for Perfalgan® can be found here: *Perfalgan, infusionsvæske, opløsning 10 mg-ml.doc*

Perfalgan® is indicated for the short-term treatment of moderate pain, especially following surgery, and for the short-term treatment of fever, when administration by intravenous route is clinically justified by an urgent need to treat pain or hyperthermia and/or when other routes of administration are not possible.

According to a European survey, 22 incidents involving overdoses of intravenous paracetamol in infants occurred from December 2003 to December 2009 (19 of them in Europe). In all cases, the overdose occurred because 10 times the prescribed dose had accidentally been given.

1) Perfalgan® is the only intravenous paracetamol product on the Danish market.

Avoid concomitant treatment with clopidogrel (Plavix®, etc.) and omeprazole/esomeprazole (Losec® and Nexium®, etc.)[1]

If patients are treated concomitantly with clopidogrel and omeprazole/esomeprazole, doctors should consider the option of using another proton pump inhibitor (PPI).

- Patients who are treated concomitantly with clopidogrel and PPIs other than omeprazole and esomeprazole can safely continue treatment.

The product information for omeprazole, esomeprazole and clopidogrel will soon be updated with the new recommendations. Please find more information about clopidogrel and omeprazole/esomeprazole here: *EMA/173011/2010.*

In May 2009, the European Medicines Agency (EMA) raised concern about a possible risk of interaction between proton pump inhibitors (PPI) and clopidogrel-containing medicines. This concern was prompted by a number of studies which suggested that the concomitant use of PPIs and clopidogrel might reduce the effectiveness of clopidogrel, decreasing its preventive effect against blood clots such as heart attacks and strokes.

EMA's Committee for Medicinal Products for Human Use (CHMP) has now analysed data from a line of new studies, leading it to restate its warning against using clopidogrel at the same time as the two PPIs: omeprazole and esomeprazole. However, based on the currently available data, the CHMP has also concluded that there are no grounds to extend the warning to other PPIs.

1) We have chosen to mention Plavix®, Losec® and Nexium® for the sake of recognisability.

Newborns at risk for persistent pulmonary hypertension if the mother has taken a serotonergic antidepressant during pregnancy

The EU Pharmacovigilance Working Party has considered new studies published in the scientific literature with regard to a possible risk for persistent pulmonary hypertension of the newborn (PPHN) when the mother has taken a serotonergic antidepressant during pregnancy.

- Physicians - midwifes, obstetricians, etc. - should pay attention to decreases in oxygen saturation caused by PPHN in newborns of mothers who have taken a serotonergic antidepressant during pregnancy.

- Doctors should inform pregnant patients who are treated with a serotonergic antidepressant to contact the hospital immediately if their newborn child shows symptoms of PPHN - e.g. if the baby starts to breathe faster and turns bluish.

The summaries of product characteristics for all serotonergic antidepressants will be updated with the new recommendations.

The recommendations apply to both SSRIs (selective serotonin reuptake inhibitors) and other antidepressants with similar serotonergic action (duloxetine, mirtazapine, venlafaxine). Further information is available at: *http://www.ema.europa.eu/pdfs/human/phvwp/17301110en.pdf.*

PPHN is a condition in which high blood pressure in the lungs prevents the newborn's blood vessels from dilating naturally, causing a sudden decrease in oxygen saturation at birth. Symptoms of PPHN usually begin within 24 hours after birth. In the general population, one to two cases of PPHN occur per 1000 births.

Still, the risk of PPHN in newborns exposed to serotonergic antidepressants is very low (approx. five cases per 1000 births).

Increased risk of cardiovascular birth defects from the use of the antidepressant fluoxetine during the first three months of pregnancy

The EU Pharmacovigilance Working Party has just finished a review of a number of studies on the use of fluoxetine during the first three months of pregnancy and the possible risk of birth defects.

The data suggest that

- the risk of having an infant with a cardiovascular defect following the use of fluoxetine during the first trimester has increased twofold from one to about two per 100 newborns.

The information will be implemented in the summary of product characteristics and package leaflet for fluoxetine-containing products.

Same risk as suspected for paroxetine

The documented risk of birth defects associated with the use of fluoxetine in the first trimester corresponds to observations on paroxetine antidepressants. Both antidepressants belong to the class of selective serotonin reuptake inhibitors (SSRIs).

No corresponding studies have been made on the use during pregnancy of the other substances in the class. It is not inconceivable that similar risks may exist for these substances.

In 2009, a total of 85,851 women aged 15 to 44 were in treatment with antidepressants acting on the serotonergic system.

The bar chart in figure A shows the number of women aged 15 to 44 in treatment with a product in the group of serotonergic antidepressants in Denmark. Please note that the same woman may have redeemed prescriptions for several products within the same class during 2009 and may therefore appear in the chart more than once.

The newest data show that SSRIs have been used in 2.4 % of all pregnancies in Denmark.

A detailed summary of the Pharmacovigilance Working Party's review of fluoxetine-containing products is available here: *Monthly report*

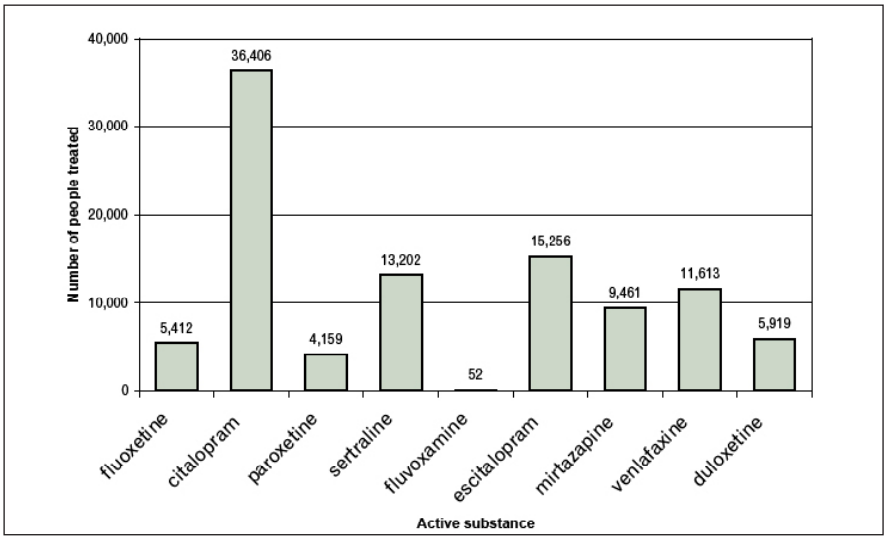

Figure A. Number of women aged 15 to 44 having redeemed a prescription for an antidepressant acting on the serotonergic system in 2009 in Denmark.

fluoxetine (Fontex, etc.)
citalopram (Cipramil, etc.)
paroxetine (Seroxat, etc.)
sertraline (Zoloft, etc.)
fluvoxamine (Fevarin, etc.)
escitalopram (Cipralex, etc.)
mirtazapine (Remeron, etc.)
venlafaxine (Effexor, etc.)
duloxetine (Cymbalta, etc.)

General precautions for the use of any SSRI:

Newborn babies of mothers having taken an SSRI at the end of pregnancy should be monitored due to the risk of symptoms of serotonergic activity or withdrawal symptoms in the newborn child. Withdrawal symptoms could be irritation, drowsiness, difficulty eating or breathing. In most cases, complications begin immediately or shortly after birth (< 24 hours).

Gadolinium-containing MRI contrast agents

On the basis of Danish ADR reports, the Danish Medicines Agency requested in 2006 the Pharmacovigilance Working Party to put the correlation between gadolinium-containing MRI contrast agents and nephrogenic systemic fibrosis on the agenda. Last year, we put it up for discussion once more to obtain harmonised European recommendations on the use of this type of agents in e.g. the elderly, newborns and patients who are to receive a liver transplant. The case was closed in March 2010.

High-risk gadolinium-containing contrast agents (Optimark®, Omniscan®, Magnevist®, Magnegita® and Gado-MRT ratiopharm®).

- Patients with severe kidney problems, patients who are scheduled for or have recently received a liver transplant and newborn babies up to four weeks of age should not be given high-risk contrast agents.
- All patients should be screened for kidney problems (s-creatinine) before they are given a high-risk contrast agent.
- Women should discontinue breast-feeding until 24 hours after a scan.

Medium-risk agents (Vasovist®, Primovist® and MultiHance®) and low-risk agents (Dotarem®, ProHance® and Gadovist®).

- Patients with severe kidney problems and patients who are scheduled for a liver transplant should not be given these agents.
- All patients should be screened for kidney problems before receiving a gadolinium-containing agent.
- The decision to continue or suspend breast-feeding for at least 24 hours after a scan should be taken by the doctor and the mother.

Please find the remaining recommendations for the use of gadolinium-containing MRI contrast at: *http://www.ema.europa.eu/pdfs/human/press/pr/73981809en.pdf*

Top 10 most frequently reported substances and consumption figures

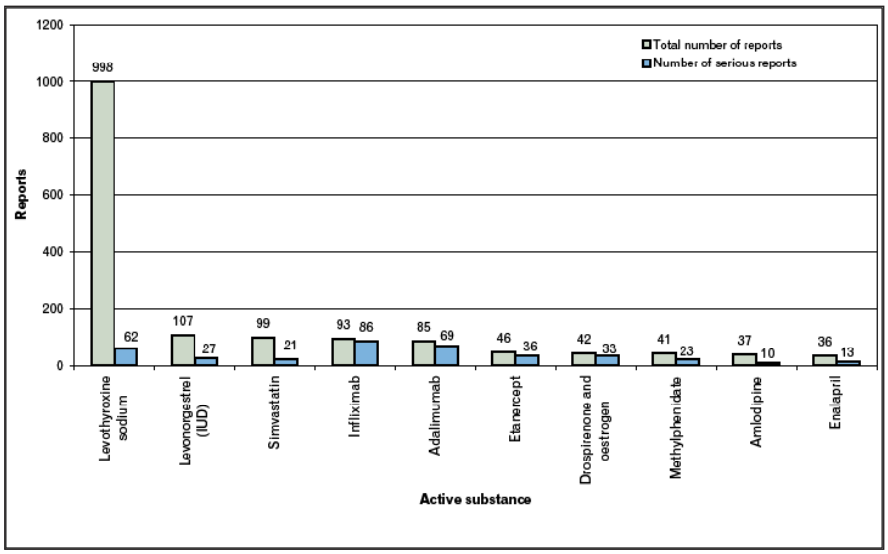

Figure X. Top 10 medicines generating the most ADR reports in Denmark (2009)

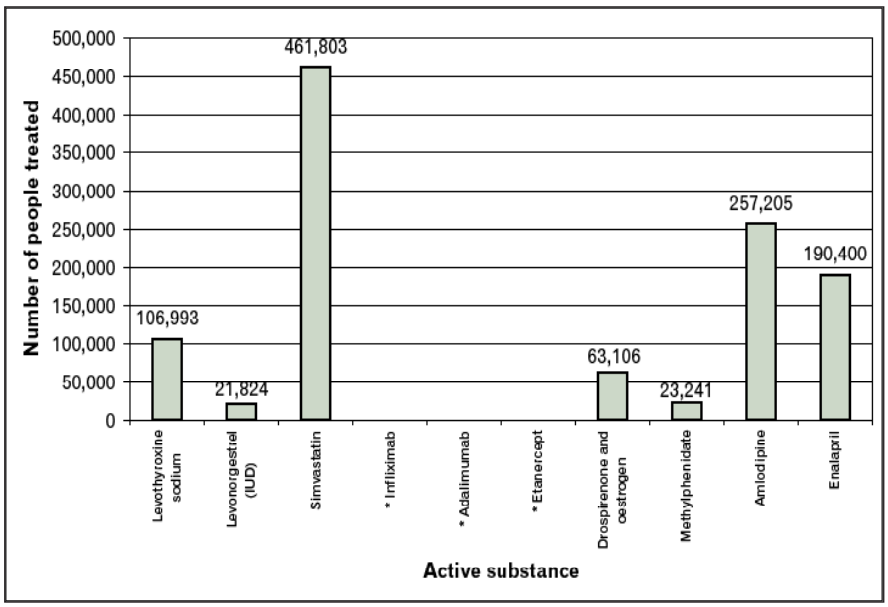

Figure Y. Number of people treated with a medicine in top 10 in Denmark (2009)

** These three drugs are so-called biological medicines, which are primarily used at hospitals, and the Register of Medicinal Product Statistics therefore does not contain exact data on the number of people treated.*

The ten active substances having generated the most ADR reports in Denmark in 2009 appear in figure X. The number of ADR reports submitted for a certain active substance or drug class (e.g. statins) should always be compared to the level of consumption. Figure Y shows the consumption of the ten active substances, where the number of people treated corresponds to the number of persons having redeemed at least one prescription for the medicine concerned in 2009. The consumption data are sourced from the Agency's Register of Medicinal Product Statistics.

You can find more information about the top 10 substances generating the most ADR reports and the Agency's pharmacovigilance activities in: *The Danish Medicines Agency's annual pharmacovigilance report 2009*

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