# Danish Pharmacovigilance Update

#9
Volume 4, 31
October 2013

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# The risk of blood clots from the use of contraceptive pills is low regardless of type

In recent years, the Danish Health and Medicines Authority has recommended using 2nd generation contraceptive pills rather than 4th generation to decrease the risk of blood clots[1].

However, the risk of blood clots is very low in general regardless of the selected type of contraceptive pill. This is confirmed by a new review from the European Pharmacovigilance Risk Assessment Committee (PRAC) assessing the risk of venous blood clots (venous thromboembolism) with contraceptive pills and other combined hormonal contraceptives (CHCs) containing oestrogen and progestogen.

### The risk of blood clots from the use of contraceptive pills is generally low

The PRAC's review confirmed that the risk of venous blood clots is low with all types of contraceptive pills and with other CHCs and that there are small differences in the risk between the CHCs depending on the type of progestogen they contain.

### Advice for doctors:

- Doctors should assess a woman's individual risk of venous blood clots prior to prescribing contraceptive pills or a CHC for the first time and regularly thereafter, as the risk changes over time. Risk factors for venous blood clots include, e.g., overweight, age above 35 years, migraine, a family history of blood clots or use of contraceptive pills within a few weeks after having given birth.
- Consider differences in the risk of blood clots between the various types of progestogen contained in contraceptive pills and other CHCs.
- It is important that the woman is informed about the risk of venous blood clots and symptoms to pay attention to. These may include, e.g., severe pain or swelling in the legs, sudden unexplained breathlessness, rapid breathing or cough, chest pain, and face, arm or leg numbness. Women developing any of these symptoms should seek medical attention immediately.

Read more in the *PRAC's* press release: *PRAC confirms that benefits of all combined hormonal contraceptives (CHCs) continue to outweigh risks*

### The PRAC's review included the following contraceptive pills

The review included all contraceptives containing low-dose oestrogen and the following progestogens: chlormadinone, desogestrel, dienogest, drospirenone, etonogestrel, gestodene, nomegestrol, norelgestromin and norgestimate. These are sometimes referred to as '3rd generation' or '4th generation' contraceptives and are available as pills, skin patches and vaginal rings.

During the review, the risk of venous blood clots with these contraceptives was compared with that of CHCs containing the progestogens levonorgestrel and norethisterone (also known as '2nd generation' contraceptives).

1) *Older contraceptive pills still pose the lowest risk of blood clots*
*Doctors in Denmark follow the recommendations for contraceptive pills*
*Danish Pharmacovigilance Update 19 August 2010*
*Danish Pharmacovigilance Update, 19 May 2011*
*Danish Pharmacovigilance Update 16 February 2012*

News from the EU

# The EU has completed the review of plasma substitutes containing hydroxyethyl starch (HES)

**The European Medicines Agency, EMA, recommends not to use HES in patients with sepsis or burn injuries or in critically ill patients and to exercise caution when using HES in other patients.**

That is the conclusion following a review of plasma substitutes containing hydroxyethyl starch (HES) for blood volume replacement in case of blood or plasma loss. The review was a follow-on to another review made earlier this year, where the European Pharmacovigilance Risk Assessment Committee (PRAC) assessed benefits and risks of the use of HES based on several new studies[1,2,3], in which treatment with HES was compared to treatment with crystalloids in critically ill patients. The studies showed that patients with serious sepsis treated with HES had an increased risk of renal injury requiring dialysis. Furthermore, two of the studies suggested that mortality is increased in patients treated with HES.

## The PRAC's first assessment of HES

Based on the available data, the PRAC concluded that HES as compared with crystalloids increases the risk of renal injury requiring dialysis and increases the mortality. The PRAC further concluded that the available data only showed a limited benefit of HES in plasma substitution and that the benefits therefore do not outweigh the known risks. Accordingly, the PRAC recommended suspension of the marketing authorisations for medicines containing HES, until the companies potentially identify a group of patients in whom the benefits of the medicines continue to outweigh the risks.

## New assessment of HES

Subsequently, the PRAC assessed new information[4,5,6], and the companies marketing HES products have undertaken to carry out new studies and other initiatives to shed light on and further limit the risk.

Based on the new assessment, the PRAC confirms that HES may still not be used in patients with sepsis or burn injuries or in critically ill patients. However, HES may continue to be used to treat hypovolaemia caused by acute blood loss in other patients, when treatment with crystalloids is not deemed sufficient and when the precautions are observed.

## Advice for doctors:

- Due to a lack of long-term safety data for the use of HES in patients undergoing surgical procedures and in patients with trauma, the expected benefits of treatment for each individual patient should be carefully weighed against the uncertainties with regard to long-term safety, and other available treatment options should be considered.
- HES should be used at the lowest effective dose for the shortest period of time. Therefore, HES should only be used in the initial phase for blood volume replacement and for a maximum of 24 hours.
- HES is contraindicated in patients with renal impairment and patients receiving dialysis, and the use of HES must be discontinued immediately at the first sign of renal injury. An increased risk of renal injury requiring dialysis is observed for up to 90 days after HES administration. Therefore, it is recommended to monitor the patients' renal function for a minimum of 90 days.
- HES is contraindicated in serious coagulopathy. HES should be discontinued at the first sign of coagulopathy, and blood coagulation parameters should be monitored carefully in case of repeated administration.

Additionally, the PRAC required that further studies be carried out by the companies on the safety and efficacy of the use of HES in elective surgery and in trauma patients.

Read more information about the review procedure on the EMA's website. *Hydroxyethyl-starch solutions (HES) should no longer be used in patients with sepsis or burn injuries or in critically ill patients – CMDh endorses PRAC recommendations*


1) Perner, A. et al. Hydroxyethyl Starch 130/0.42 versus Ringer's acetate in severe sepsis. N Engl J Med 2012; 367(2):124-134.
2) Bunkhorst, F.M. et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. N Engl J Med, 2008; 358(2):125-39.
3) Myburgh, J.A. et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care; N Engl J Med 2012; 367(20):1901-11.
4) Annane D. et al. CRISTAL: Colloids Compared to Crystalloids in Fluid Resuscitation of Critically Ill Patients: A Multinational Randomised Controlled Trial. NCT00318942. Available at: *http://clinicaltrials.gov/ct2/show/NCT00318942*
5) Siegemund M. Firstly presented at European Society of Anaesthesiology conference 2012. Basel Study for Evaluation of Starch (130;0.4) Infusion in Septic Patients:BaSES (130;0.4) Trial, listed at *http://clinicaltrials.gov/show/NCT00273728*
6) Rational Fluid Therapy in Germany (RaFTinG). Available at ClinicalTrials.gov (NCT01122277) last updated on 07 July 2011: *http://clinicaltrials.gov/ct2/show/NCT01122277?term=NCT01122277&rank=1*

News from the EU

# Risk of intraoperative floppy iris syndrome (IFIS) related to treatment with risperidone or paliperidone in patients undergoing cataract surgery

IFIS is an intraoperative complication observed during cataract surgery.

Cases of IFIS in association with the use of antipsychotics with α1-adrenergic receptor blocking activity, including risperidone are reported in literature.

An increase in the frequency of reports concerning IFIS in association with the use of risperidone has been observed during routine pharmacovigilance. During a cumulative review, six cases of IFIS were identified worldwide in association with the use of risperidone, and in two of these cases a correlation between the treatment with risperidone and IFIS was deemed likely.

**No Danish reports**

The Danish Health and Medicines Authority (DHMA) has not received reports concerning IFIS in association with the use of risperidone, paliperidone or paliperidone palmitate.

**IFIS – a rare adverse reaction from the use of risperidone**

The estimated frequency of reports concerning IFIS in association with the use of risperidone is between 1 in 1,000 and 1 in 10,000 (rare adverse reaction). There has been no reports concerning paliperidone and IFIS. However, since it is an active metabolite of risperidone the information and the advice also apply to paliperidone.

The potential benefits of discontinuation of risperidone or paliperidone prior to cataract surgery on the risk of IFIS have not been established and must be weighed against the risk of discontinuation of the antipsychotic therapy.

**Advice for doctors:**

- There is a risk of IFIS during and after cataract surgery in patients taking drugs containing risperidone, paliperidone or paliperidone palmitate.
- Since IFIS is associated with an increased number of complications in cataract surgery, patients should be questioned about current or prior use of drugs containing risperidone, paliperidone or paliperidone palmitate when recording the medical history prior to the operation.
- Cataract surgeons should approach surgery with caution. If IFIS is suspected, measures to prevent the iris from prolapsing during the cataract surgery may be required.

The summaries of product characteristics for medicines containing risperidone, paliperidone or paliperidone palmitate are being revised, and letters of the above-mentioned information have been sent to relevant doctors. The letter is also available on the DHMA's website: *List of issued DHPC letters (in Danish only)*.

# Updated recommendations for the use of intravenous iron products

The European Medicines Agency, EMA, has completed a review of the benefits and risks from the use of intravenous (IV) iron products following concerns about the risk of serious hypersensitivity reactions.

The EMA concluded that the benefits of all IV iron products continue to outweigh the risks provided that the updated recommendations are followed.

**Test doses are no longer recommended**

All IV iron products can cause potentially fatal serious hypersensitivity reactions. The reactions may occur even when a previous administration has been tolerated, including a negative test dose. On this basis, test doses are no longer recommended.

**Updated recommendations:**

- IV iron products should not be used in patients with hypersensitivity to the active substance, the product itself or one or more of its excipients. This also applies to patients with serious hypersensitivity to other parenteral iron products.
- The risk of hypersensitivity is increased in patients with known allergies (including drug allergies) and in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) as well as in patients with a history of severe asthma, eczema or other atopic allergy. In these patients, IV iron products should only be used if the benefits are clearly deemed to outweigh the potential risks.
- To minimise the risks, IV iron products should be administered in accordance with the posology and method of administration described in the summary of product characteristics for each individual product.
- IV iron products should only be administered by persons trained to evaluate and manage anaphylactic/anaphylactoid reactions and only if resuscitation equipment is immediately available.
- Patients should be informed about the risk of hypersensitivity prior to each administration. Also, patients should be informed about the relevant symptoms and asked to seek urgent medical attention if a reaction occurs.
- Patients should be closely monitored for signs of hypersensitivity during and for at least 30 minutes after each administration of an IV iron product.
- IV iron products should not be used during pregnancy unless clearly necessary. Treatment should be confined to 2nd or 3rd trimester, if the benefits are clearly deemed to outweigh the potential risks for both the mother and the foetus. The risks to the foetus may be serious and comprise foetal anoxia and distress.

The summaries of product characteristics for intravenous iron products will be updated with the above-mentioned information, and letters of information have been sent to relevant doctors. The letter is also available on the Danish Health and Medicines Authority's website: *List of issued DHPC letters (in Danish only).*

**Indication for IV iron products**

Treatment of iron-deficiency anaemia.

- When oral iron products cannot be used, or in case of lack of efficacy
- Where there is a clinical need to deliver iron rapidly.

The diagnosis of iron-deficiency anaemia should be based on relevant laboratory tests.

News from the EU

## Knowledge of the use of valproate during pregnancy will be reviewed in the EU

The European Pharmacovigilance Risk Assessment Committee (PRAC) has started a review of data concerning the use of valproate during pregnancy.

Valproate is approved for the treatment of epilepsy and manic episodes in bipolar disorder. It has been known for some time that the use of antiepileptics in pregnant women increases the risk of birth defects in their children and that valproate may be associated with a higher risk of certain malformations than other antiepileptics. It is also known that development may be delayed in children of mothers who were treated with valproate during pregnancy.

The EU review is initiated now because recently published studies have demonstrated that some children may experience long-lasting problems in development or autism when the mother was treated with valproate during pregnancy.

Read more about the PRAC's review here. *Valproate and related substances*

## Common labelling of medicines under additional monitoring in the EU

As of autumn 2013, the EU has introduced a new process for labelling of medicines that are being monitored particularly closely by the regulatory authorities. Medicines under additional monitoring have a black inverted triangle displayed in their package leaflet and summary of product characteristics together with the following sentence:

▼ This medicinal product is subject to additional monitoring.

### Medicines under additional monitoring

All medicines are carefully monitored after being placed on the EU market. If a medicine is labelled with the black triangle, this means that it is being monitored even more intensively than other medicines. This is generally because there is less information available on the medicine in question than on others, for example because it is new to the market or there is limited data on its long-term use.

It does not mean that the medicine is unsafe.

Doctors and patients are encouraged to be particularly aware of detecting and reporting potential adverse reactions from medicines labelled with ▼.

### A medicine becomes subject to additional monitoring in the following cases:

- It contains a new active substance approved in the EU after 1 January 2011
- It is a biological medicine, such as a vaccine or a medicine derived from plasma (blood), for which there is limited post-marketing experience
- It has been given a conditional approval (i.e. the company that markets the medicine must provide more data about it) or approved under exceptional circumstances (i.e. there are specific reasons why the company cannot provide sufficient data about the medicine)
- The company that markets the medicine is required to carry out additional studies, for instance to provide more data on long-term use of the medicine or on a rare adverse reaction seen during clinical trials.

Other medicines can also be placed under additional monitoring, based on a decision by the European Pharmacovigilance Risk Assessment Committee (PRAC).

### EU list of medicines under additional monitoring

A European *list of medicines under additional monitoring* is available.

The European Medicines Agency, EMA, first published this list in April 2013. It is reviewed every month by the PRAC.

Read more about medicines under additional monitoring on the Danish Health and Medicines Authority's website. *Medicines under additional monitoring*

# Report of cardiac arrest in association with the use of flecainide (Tambocor®)

In August 2013, the Danish Health and Medicines Authority (DHMA) received an adverse reaction report concerning a young patient who had a cardiac arrest 12 hours after taking 200 mg Tambocor®. The patient was resuscitated and functions well today.

For six months prior to having the cardiac arrest, the patient had been treated with Tambocor® several times due to episodes of atrial fibrillation. Tambocor® was initiated during hospitalisation, and the patient had been monitored following administration of the product. The treatment showed good efficacy, and the patient was then allowed to self administer the medicine at home.

**Reports of adverse reactions involving the heart in association with the use of flecainide**

The DHMA has received a total of three reports concerning persons who have had a cardiac arrest followed by resuscitation in association with the use of flecainide.

Four other reports received by the DHMA concerned persons who died suddenly in association with the use of flecainide. One of these reports describes that the patient most likely died from a myocardial infarction, and another one describes that the patient most likely died from an AV block. The remaining two reports do not provide any further explanation.

Furthermore, the DHMA has received 11 reports concerning patients who experienced adverse reactions involving the heart without having a cardiac arrest. Most of these reports concerned tachycardia.

Adverse reactions such as second or third-degree AV block, tachycardia and cardiac arrest are known adverse reactions from the use of flecainide.

**Advice for doctors:**

- For patients with AV nodal reciprocating tachycardia, arrhythmias associated with Wolff-Parkinson-White Syndrome and similar conditions with accessory pathways and paroxysmal atrial fibrillation and in patients with disabling symptoms, the treatment with oral flecainide should take place under direct hospital or specialist supervision.
- For patients with other indications, initiating treatment and changing the dose should take place in a hospital under ECG monitoring to reveal a proarrhythmic effect, if any, as well as plasma level monitoring.
- Continuous ECG monitoring is recommended for all patients receiving a bolus injection.
- Electrolyte disturbances should be corrected before using flecainide. Severe bradycardia and pronounced hypotension should also be corrected before using flecainide.
- Plasma level monitoring and ECG control are recommended at regular intervals (ECG control every month and long-term ECG every third month) during treatment. During the initial treatment phase and when increasing the dose, an ECG should be carried out every 2-4 days.

**Indication for flecainide**

Symptomatic supraventricular arrhythmias where other treatment has proven ineffective. Life-threatening ventricular arrhythmias.

News from the Danish Health and Medicines Authority

# Granuloma formation following vaccination with aluminium adjuvant vaccines – a known, but rare adverse reaction

It appears from the summary of product characteristics for several vaccines that granuloma – an itchy long-lasting nodule formation at the injection site – may occur. This granuloma is most often caused by the aluminium content of the vaccine.

Some vaccines contain aluminium with the purpose of enhancing the vaccine stimulation of the immune system. For example, the DTaP-IPV/Act-Hib vaccine contains 1 mg per dose. Internationally (the WHO and the FDA), the recommendation is to restrict the aluminium content to 1.25 mg per dose.

Occurrence of granulomas following vaccination with vaccines containing aluminium is a known, rare and most often non-serious adverse reaction[1].

## The granuloma formation may be due to allergy

The granuloma formation is thought to be due to allergy (type IV) to aluminium[2,3]. The granuloma typically appears three months after the vaccination, but may appear within a few weeks to years after the vaccination.

The granuloma is often very itchy. There may be increased hair growth, changed pigment content or eczema in the skin covering the granuloma.

The granuloma may be present for years, but the itching most often slowly subsides. The aluminium allergy also seems to be reduced over time in most people. A Swedish study[4] comprising 76,000 children showed that approx. 1% of the vaccined children developed a granuloma. Of the children with granulomas, 76% were allergic to aluminium. When testing the children five years or more after the vaccination, aluminium allergy was no longer detectable in two out of three children. The more time passed, the higher the likelihood that the allergy test with aluminium was negative.

It is not clear how many of those, who developed a granuloma once, will develop another granuloma if they are vaccinated with a vaccine containing aluminium again. In another Swedish publication[5] comprising 40 children showing symptoms of aluminium allergy following vaccination, 25 were vaccinated again at a later date with a vaccine containing aluminium. Of these children, 2 (8%) developed granulomas again, whereas the others tolerated the vaccination without granuloma formation.

## Allergy to other products containing aluminium

Aluminium sensibilisation may cause contact allergy to products containing aluminium such as certain creams including certain sun creams, certain ear drops and deodorants. Also, itching has been reported following intake of raisins – a food containing aluminium. Aluminium allergy in adults is very rare, and there is a lot to suggest that aluminium allergy in children is temporary in most cases.

Nightly itching can be reduced by letting the child sleep in a cool place. It is important to prevent scratching of the skin during the day and at night-time, e.g. by using a bandage or patch. Treatment with an adrenal cortex hormone cream for periods of time can be an option.

### Adverse reaction reports concerning vaccination granulomas

In the period 1 January 2008 through 30 September 2013, the Danish Health and Medicines Authority received a total of 89 adverse reaction reports concerning vaccination granulomas and related symptoms including 59 non-serious reports. Six of the reports concern granulomas occurring in adults following vaccination with Gardasil® or DTaP-IPV Booster®. In 17 cases concerning vaccination granulomas, the Danish Patient Insurance Association compensated the patients.

1 A serious adverse reaction is defined as an adverse reaction which is fatal, life-threatening, causes or prolongs hospitalisation, or causes permanent or significant disability or inability to work, or which is a congenital anomaly or birth defect cf. section 3(4) of Danish executive order no. 826 of 1 August 2012 on the reporting of adverse reactions from medicinal products etc. (bekendtgørelse nr. 826 af 1. august 2012 om indberetning af bivirkninger ved lægemidler m.m.) (in Danish only).

2 The Statens Serum Institut, National Institute for Health Data and Disease Control, EPI-NEWS, No. 5, 2003.

3 The Danish National Allergy Research Centre, *http://www.videncenterforallergi.dk/english.html/*, June 2013

4 Lidholm, A.G. et al. Unexpected loss of contact allergy to aluminium induced by vaccine. Contact Dermatits 2013, 68, 286-292.

5 Bergfors, E. et al. Sixty-four children with persistent itching nodules and contact allergy to aluminium after vaccination with aluminium-absorbed vaccines-prognosis and outcome after booster vaccination. Springer-Verlag 2012.

# Always remember to include both the product name and batch number when submitting reports of suspected adverse reactions from vaccines and biological drugs

In order for the Danish Health and Medicines Authority (DHMA) to be able to monitor the safety of medicinal products in the best possible way, it is especially important that monitoring can take place at the product level when it comes to vaccines and biological drugs. Therefore, always remember to include both the name (or the manufacturer) of the drug/vaccine and the specific batch number when reporting suspected adverse reactions from vaccines and/or biological drugs.

**You should also inform patients about the product name and batch number**

It will also be good practice to inform patients about the product name and batch number in connection with a vaccination or when patients are treated with a biological drug. This will enable the patients and their relatives to submit more satisfactory reports of suspected adverse reactions to the DHMA.

**Biological drugs and vaccines differ significantly from chemically manufactured medicines**

Biological drugs and vaccines differ fundamentally from chemically manufactured medicines when it comes to complexity. In contrast to most drugs, which consist of small molecules, the properties of biological drugs are a function of their specific manufacturing process as well as their active substances.

There is a wide range of vaccines and biological drugs, and many manufacturers produce the same active substance. The products comprise a range of biosimilar drugs, various vaccines which protect against a specific infection, and other products such as human immunoglobulin.

Unlike most common, generic drugs, these products do not have identical properties. Therefore, it is very important to monitor safety at product level. Additionally, biological drugs may vary between batches. Therefore, it is essential that your reports to the DHMA contains information about the batch numbers.

Report suspected adverse reactions from medicines and vaccines to the DHMA at *http://sundhedsstyrelsen.dk/en/medicines/safety/side-effects/report-a-side-effect-or-incident/humans*

Danish Pharmacovigilance Update is published by the Danish Health and Medicines Authority
http://www.sundhedsstyrelsen.dk/English.aspx
Editor-in-Chief:
Henrik G. Jensen (HGJ)
Editor:
Nina Vucina Pedersen (NVP)
ISSN 1904-2086