Danish Pharmacovigilance Update #6

Volume 5
June
2014

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Potentially life-threatening accidental exposure to fentanyl patches (Durogesic® etc.)

The Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency recently reviewed the safety of fentanyl patches following incidents of accidental exposure to fentanyl pain-relief patches.

Accidental exposure is not a new phenomenon, and reports are still submitted on accidental exposure to transdermal fentanyl in opioid-naive patients. Cases reported outside Denmark have involved children and with fatal outcomes.

Pain-relief with fentanyl patches is still relevant when opioid formulations with long-term efficacy are needed to treat patients with chronic pain, especially patients who have difficulty taking oral medication, including prolonged release morphine. Therefore, it is paramount that doctors and nursing staff pay attention to the below precautions for use.

Precautions to avoid accidental transfer of patches to other patients

- Before, during and after treatment, accidental transfer of a patch to another patient should be avoided, among other things by ensuring that the entire patch sticks well to the skin.
- When treating e.g. children and demented patients, the patch should be placed at a site where the patient cannot remove it himself/herself.
- Used patches should be folded across the middle immediately after use so that the adhesive side of the patch adheres to itself. After 72 hours, used patches still contain a significant amount of fentanyl. The patch should therefore be placed in a plastic bag and put in a waste bin immediately after removal, or should be placed in another waste container out of children's reach.
- Hand over unused fentanyl patches to a pharmacy or hospital.
- If a patch is accidentally transferred to the wrong person, it should be removed immediately. Delayed symptoms (nausea, vomiting, affected breathing and affected consciousness) may develop. If symptoms develop, the patient should be admitted to hospital immediately.

Consumption of fentanyl patches in Denmark

Both the hospital sector and the primary sector have seen slightly decreased sales of fentanyl patches in recent years. In 2013, 226,700 defined daily doses (DDD) were sold in the hospital sector, and 3,153,700 DDD were sold in the primary sector (Source: Medstat).

Adverse reactions related to fentanyl patches reported to the DHMA

As at 14 May 2014, a total of 134 adverse reactions involving fentanyl patches had been reported to the Danish pharmacovigilance database. None of the reports mention accidental exposure.

In 2012, the adverse reaction definition was expanded to cover noxious and unintended reactions resulting from inappropriate use, medication errors and off-label use of medicines.

In June 2014, a medication error was reported describing an elderly, demented resident at a nursing home who, on two occasions, had removed the fentanyl patch and put it in the mouth. On both occasions, the resident apparently had had the patch in the mouth for two hours at most. After the second time, hospitalisation was required.

Ten reports describe cases of adhesion problems related to fentanyl patches with either poor or excessive adhesiveness. Poor adhesiveness may lead to serious adverse reactions as patches lying around may stick to the wrong persons, exposing them accidentally to fentanyl.

Adverse events related to fentanyl patches reported to the Danish National Agency for Patients' Rights and Complaints

From September 2010 to April 2014, three events involving fentanyl patches and accidental exposure were recorded in the Danish Patient Safety Database under the Danish National Agency for Patients' Rights and Complaints.

The first event involved a mix-up of packing slips on two packages dispatched by a pharmacy to an OTC outlet whereby fentanyl patches for an elderly patient were delivered to a 12-year-old child resulting in overdose. In hospital, the child received treatment against severe fentanyl overdose and has since recovered.

Indication for fentanyl patches

Adults: Severe chronic pain, which can be adequately managed only with opioid analgesics.
Children: Long term management of severe chronic pain in children receiving opioid therapy from 2 years of age.

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In the second event, homecare services found a fentanyl patch stuck to the patient's arm the day after being discharged from hospital. According to the patient's medication chart, the patient was being treated with oxycontin and paracetamol tablets for pain-relief, whereas fentanyl was not prescribed on the medication chart. The patient did not appear to be affected by the increased morphine dose. No date appeared on the patch, so there was no way of telling for how long the patch had adhered to the skin.

The third event involved a GP who had accidentally prescribed fentanyl to the wrong patient whose name resembled the name of the patient for whom the medicine was intended. The error was discovered in time, and no harm was done.

Since it must be presumed that both medication errors and adverse reactions are underreported, the number of cases do not reflect the true magnitude of the problem. Mix-ups and sectoral crossings still play a significant role in medication errors.

In June, letters have been sent out to relevant doctors to raise awareness on the problem. In parallel, the pharmaceutical companies involved have been requested to investigate ways to improve the visibility of the patches.

Medication errors must be reported to the Danish National Agency for Patients' Rights and Complaints (*www.patientombuddet.dk*), and adverse reactions should be reported to the DHMA (*www.meldenbivirkning.dk*). The DHMA forwards all reports of suspected adverse reactions caused by medication errors to the Danish National Agency for Patients' Rights and Complaints in depersonalised form, just as the Danish National Agency for Patients' Rights and Complaints makes its reports available to the DHMA.

Combined use of medicines affecting the renin-angiotensin system (RAS) is restricted

The European Medicines Agency restricts combined use of medicines acting on RAS.

Several of these medicines have been used concomitantly in combination therapy with the purpose of increasing efficacy. However, a review of the newest data suggests that most patients do not experience any increased effect. By contrast, combination therapy could increase the patients' risk of low blood pressure, elevated potassium levels in the blood and kidney damage.

Consequently, combination therapy affecting the RAS is no longer recommended. This particularly applies to the combination of angiotensin II antagonist/ACE inhibitor in patients with diabetes-related kidney problems (the combination of aliskiren and either an angiotensin II antagonist or an ACE inhibitor is already contraindicated in patients with impaired renal function or diabetes).

In situations where combined use is considered absolutely essential, treatment must be carried out by specialist healthcare professionals, closely monitoring the renal function, electrolytes and blood pressure. Such supervised use also includes the therapeutic indication where e.g. valsartan is used as add-on therapy to ACE inhibitors in patients with heart failure.

Doctors should be aware of the following:

- Any combined use affecting the RAS consisting of angiotensin II antagonists, ACE inhibitors or aliskiren is not recommended to any patients. In particular, angiotensin II antagonists and ACE-inhibitors should not be used concomitantly in patients with diabetic nephropathy.

RAS-acting medicines belong to three main classes: angiotensin II inhibitors, angiotensin-converting enzyme inhibitors (ACE)-inhibitors and renin inhibitors.

The medicines in these three classes may be used for one or more of the following indications: Hypertension. Heart failure. Reduced left ventricular function and/or clinical signs of heart failure after AMI.

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Furthermore, the existing contraindications on the use of aliskiren with either an angiotensin II antagonist or an ACE inhibitor in patients with diabetes mellitus or moderate to severe renal impairment (GFR < 60 ml/min/1.73 m^2) are confirmed.

- In individual cases where combined use of an angiotensin II antagonist and ACE inhibitor is considered absolutely essential, it must be carried out by specialist healthcare professionals, with close monitoring of renal function, electrolytes and blood pressure.
- Treatment necessitating careful monitoring also includes the therapeutic indication where e.g. valsartan is used as add-on therapy to an ACE inhibitor in patients with heart failure. Combination treatment in patients with chronic heart failure should be limited to those intolerant to mineralocorticoid antagonists and with persistent symptoms despite other optimal therapy.
- The presently available efficacy data indicate that combination therapy does not provide significant benefit in the general patient population, although it is likely that specific sub-populations may benefit of combination therapy. In patients with heart failure there is some evidence that the addition of a second RAS-acting agent may reduce hospital admissions.

The recommendations are based on a detailed review of the available data, including clinical trials, meta-analyses and publications, as well as advice from an expert group on cardiovascular medicine.

Read more about the background and the process on the EMA website: *Combined use of medicines affecting the renin-angiotensin system (RAS) to be restricted – CHMP endorses PRAC recommendation*.

The summaries of product characteristics of all medicines concerned will be updated accordingly.

EU starts review of cardiovascular risks from long-term use with high doses of ibuprofen

The Pharmacovigilance Risk Assessment Committee (PRAC) has started a review to evaluate the cardiovascular risks with systemic use of ibuprofen medicines. The review focuses on high-dose ibuprofen (2400 mg daily) taken over long periods.

It is not suspected that normal use of ibuprofen to relieve mild pain is associated with an increase risk.

The class of pain-relieving medicines known as NSAIDs (nonsteroidal anti-inflammatory drugs), which ibuprofen belongs to, has been monitored closely for many years with respect to the risk of cardiovascular effects. The recommendations for the NSAID products have been tightened previously, primarily as concerns the type called COX-2 inhibitors, and as late as last year, restrictions were imposed on diclofenac.

Now, new data from particularly a meta-analysis published in 2013[1] have prompted further investigations into the cardiovascular risk of ibuprofen.

Read EMA's press release here: *European Medicines Agency starts review of ibuprofen medicines*.

Previous information on the safety of diclofenac is available in *Danish Pharmacovigilance Update, August 2013*

1 Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Coxib and traditional NSAID Trialists' (CNT) Collaboration. The Lancet, Volume 382, Issue 9894, Pages 769 - 779, 31 August 2013

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EU's list of recommendations on safety signals

As part of routine surveillance of medicines in the EU, the Pharmacovigilance Risk Assessment Committee (PRAC) assesses signals of possible adverse reactions every month to determine whether further measures are needed to improve medicines safety[1].

The list of signals leading PRAC to recommend further measures is published on the website of the European Medicines Agency (EMA) every month.

At the PRAC meeting in May, no recommendations were made to change any product information or initiate other risk minimisation measures.

See the complete list of signals on the website of the European Medicines Agency: *List of safety signals discussed since September 2012 (Excel file)*.

1 The fact that a signal has been assessed does not mean that there is a causal link to the medicine.

Dose errors involving fosphenytoin (Pro-Epanutin)

The Danish National Agency for Patients' Rights and Complaints has investigated 16 events from the Danish Patient Safety Database that all concern confusion about the use of fosphenytoin for seizures. Five of the 16 reports involved children. Whereas most of the events did not cause harm to patients, one event resulted in cardiac arrest and another in intoxication causing severe effect on the liver, kidneys and muscle tissue damage among other things.

Pro-Epanutin dosing

Pro-Epanutin, the only fosphenytoin-containing product in Denmark, is a concentrate for solution for infusion/injection, which is used in acute situations in connection with e.g. fever cramps in children or status epilepticus.

Pro-Epanutin contains fosphenytoin, which is converted into the active substance phenytoin upon administration, but not in the ratio 1:1.

1 ml of Pro-Epanutin contains 75 mg of fosphenytoin sodium, which corresponds to 50 mg PE (phenytoin sodium equivalents) = 50 mg of phenytoin sodium.

Problems increasing the risk of dose errors

- The staff applies doses, believing that fosphenytoin and phenytoin are the same substance.
- The strengths for both fosphenytoin and phenytoin are imprinted on the Pro-Epanutin label. When diluting and dosing, the two strengths add to confusion.

Another risk factor is that Pro-Epanutin is rarely used, and that some departments do not have it as standard. Quite many staff members therefore do not know the product, which adds further to the risk of dose errors. As mentioned, Pro-Epanutin is used in acute situations where quick action is needed. In such situations, uncertainty may arise when having to convert fosphenytoin to phenytoin equivalents.

The DHMA and the Danish National Agency for Patients' Rights and Complaints recommend healthcare professionals to:

- Pay special attention to the risk of giving the wrong dose.
- Go through the newest package leaflet or summary of product characteristics and update the department's instructions according to the applicable product information.
- Raise awareness on the safety of handling medicines in general.

Pro-Epanutin must always be prescribed and dispensed as phenytoin sodium equivalents (PE).

Preventive measures

The product labelling complies with the applicable standards, but the DHMA has opened dialogue with the pharmaceutical company and the other European drug regulatory authorities to discuss possibilities for further preventative measures related to the product.

For further information, also see the announcement in Danish by the Danish National Agency for Patients' Rights and Complaints: *Confusion about the dosing of Pro-Epanutin (fosphenytoin) (Danish title: Tvivl om dosering af Pro-Epanutin (fosphenytoin))*.

Olanzapine prolonged-release injection (Zypadhera®) and post-injection syndrome

In April, the DHMA received an adverse reaction report concerning a patient with bipolar affective disorder. The patient had received an injection with Zypadhera®, a prolonged-release product, which contains the antipsychotic medicine olanzapine. Afterwards, the patient became heavily sedated and could not be waked up in the following 24 hours. The patient recovered after that.

Post-injection syndrome

During clinical trials, some patients presented with symptoms consistent with overdose following an injection of olanzapine. These reactions occurred in <0.1 % of injections and in approx. 2 % of patients. Most of these patients developed symptoms of sedation (ranging from mild in severity up to coma) and/or delirium (including confusion, disorientation, agitation/anxiety and other cognitive impairment). Other symptoms observed included extrapyramidal symptoms, dysarthria, ataxia, aggression, dizziness, weakness, hypertension and convulsion.

In most cases, the initial signs and symptoms related to this reaction appeared within 1 hour following injection, and in all cases recovery occurred within 24-72 hours.

Reports of post-injection syndrome associated with olanzapine treatment

The DHMA has received a total of six adverse reaction reports describing post-injection syndrome related to olanzapine-containing medicine.

The reports of post-injection syndrome largely correspond to the experience from the clinical rials.

Doctors should be aware of the following:

- Patients should be informed of this potential risk and advised that they should be observed in a healthcare facility for 3 hours every time the product is given. If an overdose is suspected, close medical supervision and monitoring should continue until examination indicates that signs and symptoms have resolved. The 3-hour observation period should be extended as clinically appropriate for patients who exhibit any signs or symptoms consistent with olanzapine overdose.

- Immediately prior to leaving the healthcare facility, it should be confirmed that the patient is alert, oriented, and absent of any signs and symptoms of overdose. For the remainder of the day after injection, patients should be advised to be vigilant for signs and symptoms of overdose secondary to post-injection adverse reactions, be able to obtain assistance if needed, and should not drive or operate machinery.

- If parenteral benzodiazepines are essential for management of post-injection adverse reactions, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Death reported as suspected adverse reaction to Zypadhera® in the USA

In June 2013, the DHMA reported that the U.S. Food and Drug Administration, FDA, had received reports of two unexplained deaths. Both patients had been given an injection with Zypadhera® against schizophrenia three to four days before they died. Blood tests from the deceased patients showed high concentrations of olanzapine, but it could not be clarified whether the deaths and the medicine were related. Read the announcement in Danish from June 2013 on our website: *The FDA investigates the safety of schizophrenia medicine Zypadhera (Danish title: 'FDA undersøger sikkerheden ved skizofreni-medicinen Zypadhera')*.

The DHMA is awaiting the conclusion from the FDA's investigation and concurs with the FDA and the European Medicines Agency (EMA) that the guidelines described in the current product information concerning post-injection syndrome are adequate at present.

Indication for olanzapine
Maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

All cases referred to in this article originate from the Danish Health and Medicines Authority's database of adverse drug reactions. 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.

Childhood vaccinations and adverse reactions in Q1 of 2014

Every three months, a vaccination panel reviews and assesses reports of suspected adverse reactions to vaccines included in the Danish immunisation programme. In the following, we go through the results of the assessment in the first quarter of 2014.

We published a separate review of reports of suspected adverse reactions to the HPV vaccine in *Danish Pharmacovigilance Update, May 2014.* These reports are therefore not included in this review.

From 15 January 2014, the DTaP-IPV/-Hib vaccine (SSI[1]) is temporarily replaced with a hexavalent vaccine (Infanrix hexa®) which, apart from protecting against diphtheria, tetanus, pertussis, polio and haemophilus influenza type B, also protects against hepatitis B (read more in *EPI-NEWS, week 50 2013* from SSI). Children who initiated vaccination under the childhood immunisation programme before 15 January 2014 should to the extent possible conclude vaccination with the vaccine initially given (DTaP-IPV/Hib (SSI)). In other words, there will be a temporary period during which different vaccines will be given depending on how far children have come in the immunisation programme (see EPI-NEWS, week 50 2013).

Infanrix hexa® has never before been used in the Danish childhood immunisation programme and is therefore subject to stricter reporting requirements, which means that doctors are obliged to report all suspected adverse reactions to this vaccine.

Reports in Q1 of 2014

The DHMA received a total of 46 adverse reaction reports in the first quarter of 2014. 12 (26 %) of the reports were classified as serious[2]. Table 1a shows the distribution between serious and non-serious ADR reports.

Three ADR reports concerned adults who received the vaccine against pneumococcus or the MMR vaccine. The remaining 43 reports described suspected adverse reactions in people under the age of 18 years. All serious reports involved persons under 18 years of age. One report may cover several suspected adverse reactions. Table 1b shows the number of suspected adverse reactions reported for each vaccine.

Review of non-serious ADR reports

A total of 34 (74 %) of the reports were classified as non-serious. 16 of them concerned the development of granuloma as suspected adverse reactions in connection with vaccination. Aluminium allergy was not reported as a suspected adverse reaction in any of these 16 cases.

Other suspected adverse reactions reported were local reactions at the injection site, general malaise, fever and pain. These adverse reactions are all known and described in the vaccines' summaries of product characteristics.

Vaccine	Serious	Non-serious	Total
DTaP-IPV Booster	1	2	3
DTaP-IPV/Act-Hib and DTaP-IPV Booster	1		1
DTaP-IPV/Act-Hib	7	13	20
DTaP-IPV/Act-Hib and Prevenar13/Prevenar	2	6	8
Prevenar 13	1	3	4
M-M-RVaxpro	0	5	5
Infanrix HEXA	0	1	1
Priorix	0	3	3
Pneumovax		1	1
Total	**12**	**34**	**46**

Table 1a. Reports broken down by severity in the first quarter of 2014

1 Statens Serum Institut, National Institute for Health Data and Disease Control (SSI)

2 A report is serious when one or more of the adverse reactions are serious. A serious adverse reaction caused by a medicine for human use is a reaction that results in death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, or which results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

Vaccine	No. of ADRs
DTaP-IPV Booster	13
DTaP-IPV/Act-Hib	87
Prevenar13	25
Prevenar	2
Priorix	6
Pneumovax	3
MMR vaxpro	9
Infanrix Hexa	2
Total	**147**

Table 1b. Number of suspected adverse reactions reported for individual vaccines in the first quarter of 2014.

One single report concerned the Infanrix Hexa® vaccine and described a child who had fever and vomited after vaccination. These are adverse reactions that are described in the summary of product characteristics for Infanrix Hexa®.

Among the unexpected adverse reactions reported were pain in the throat after vaccination with Prevenar 13 and affected vision after Priorix vaccination.

Review of serious reports

The DHMA assesses causality for the serious ADR reports. A causality between the vaccine and a suspected adverse reaction has been assessed in the following way:

- Possible
- Less likely
- Not possible to assess based on the available information

Reports of aluminium allergy and granuloma

Ten of the total 12 serious reports concerned aluminium allergy and the formation of granuloma as suspected adverse reactions. In nine of the reports, the DTaP-IPV/Act-Hib vaccine was suspected to have caused the adverse reactions. In two of these cases, the Prevenar 13 vaccine was also suspected. In the last of the ten reports, only the DTaP-IPV Booster vaccine was suspected as cause.

The granuloma developed at varying intervals after the vaccinations, and the exact date for reaction onset is often not evident from the reports.

Seven of the ten reports we received from the Danish Patient Compensation Association, the others from practising dermatologists or general practitioners.

A causality between the development of aluminium allergy and granuloma and the vaccines is considered possible.

Report on lack of efficacy

A report concerned a 1-year-old girl who developed pertussis despite having completed the immunisation programme. The vaccine does not offer full protection, which explains why there are cases of pertussis among vaccinated children.

The last report described a 10-month-old child who two days after vaccination developed severe middle ear infection. Since between 60 % and 80 % of children have at least one episode of middle ear infection before the age of 1 year (*www.uptodate.com*), it is considered most likely that it was a case of coincidence. Causality is therefore considered less likely.

Conclusion on Q1 2014

The number of reports on vaccines in the childhood immunisation programme is fairly steady compared to the second half of 2013 when we received 91 reports of which 37 were serious. 14 of the serious reports involved aluminium allergy and/or granuloma.

In this quarter, there is an overweight of granuloma and aluminium allergy as suspected adverse reactions.

It is likely that this overweight was spurred by an article about the issue in Danish Pharmacovigilance Update in October 2013 and by several discussions about the possible causality across social media.

It was assessed that there could be a possible causal relationship between vaccination and the reported cases of aluminium allergy and granuloma.

The adverse reactions in the non-serious reports are largely well-known and are primarily described as local reactions at the injection site, general malaise, fever and pain.

The Danish Health and Medicines Authority assesses that the benefits of the vaccines still outweigh the possible risks.

All cases referred to in this article originate from the Danish Health and Medicines Authority's database of adverse drug reactions. 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.

Short news

Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been (or soon will be) sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- Antiepileptic medicine midazolam (Buccolam): Small risk of contaminated Buccolam batches

- Anti-anginal medicine ivabradine (Corlentor/Procoralan): Reminder about the conditions for use

Also see the article in *Danish Pharmacovigilance Update, May 2014*.

- Iron preparation ferumoxytol (Rienso): Serious sensitivity reactions

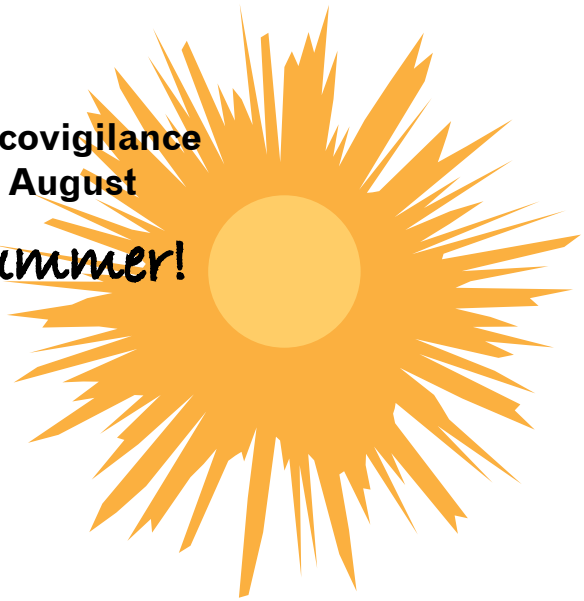
Also see the article in *Danish Pharmacovigilance Update, May 2014*.

- Pain-relieving transdermal fentanyl: Potentially life-threatening injuries may occur as a result of accidental exposure (read the article on page 2 of this issue of Danish Pharmacovigilance Update).

The DHPCs are available in Danish at the DHMA website:
List of circulated DHPCs.

Next Danish Pharmacovigilance Update will be out in August

Have a nice summer!



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

Sundhedsstyrelsen
Danish Health and Medicines Authority