Danish Pharmacovigilance Update 11

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

The most important safety signals discussed on the PRAC meeting in November 2014 concern the following products:

- **Dimethyl fumarate** – Progressive multifocal leukoencephalopathy (PML)
- **Leuprorelin** – Medication error – wrong technique in drug usage process

See EU's list of recommendations on safety signals: *PRAC recommendations on signals*.

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

Childhood vaccinations and reported suspected adverse reactions in Q3 of 2014

The DHMA continually analyses reports of suspected adverse reactions to vaccines in the Danish childhood immunisation programme, and every three months these reports are reviewed and assessed by a vaccination panel set up by the DHMA. The panel is composed of experts from relevant clinical settings in Denmark.

Here are the results of the review for Q3 2014

Since there has been much attention on adverse reactions to the HPV vaccine, our review falls into two sections:

1. A review of the ADR reports related to vaccines in the childhood immunisation programme – excluding the HPV vaccine.

2. A review of the ADR reports related to the HPV vaccine.

The review covers primary vaccinations in the childhood immunisation programme as well as booster vaccines (re-vaccination).

ADR reports about vaccines in the childhood immunisation programme Q3 of 2014

In the third quarter of 2014, the DHMA received a total of 60 reports about vaccines included in the childhood immunisation programme (the HPV vaccine is excluded in this figure). 29 of them were classified as serious[1].

Table 1a shows the number of ADR reports classified as serious and non-serious, respectively.

Vaccine	Serious	Non-serious	Total
DTaP-IPV Booster	2	2	4
DTaP-IPV /Act-Hib	14	9	23
DTaP-IPV /Act-Hib / MMR vaxpro	1	1	2
DTaP-IPV /Act-Hib / MMR vaxpro / Prevenar 13	0	1	1
DTaP-IPV /Act-Hib / Prevenar 13	9	4	13
Infanrix Hexa	1	4	5
Infanrix Hexa / Prevenar 13	0	1	1
MMR vaxpro	0	4	4
Pneumovax	1	0	1
Prevenar 13	1	0	1
Priorix	0	5	5
Total	29	31	60

Table 1a. Reports broken down by severity.

[1] 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.

Review and assessment of the serious reports
When we assess the serious ADR reports, we investigate whether it is likely that there is a causal connection to the vaccine.

The result of our causality assessment is split into three categories:

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

Vaccine	ADR description	Assessment and causality
DTaP-IPV Booster	Anaphylaxis	Only few details are available, but since anaphylaxis is a known adverse reaction, causality is considered **possible**
DTaP-IPV/Act-Hib	Four cases of vaccine failure (patients developed pertussis)	All had received three vaccine doses. It is known that the vaccine does not offer full protection.
Infanrix Hexa	A patient was briefly admitted to hospital with urticaria	This is a known and thus **possible** adverse reaction to the vaccine
Pneumovax	Pain and paresis of the arm, perhaps after an allergic reaction	Local reactions are well-known, and since there is a close temporal relationship, causality is considered **possible.**

Table 1b: Description of the adverse reactions described in the serious ADR reports and subsequent causality assessment.

In addition, there are a total of 22 reports of granuloma and aluminium allergy. The vast majority of them ascribe these reactions to DTaP-IPV/Act-Hib, but Prevenar 13 (10) and MMR Vaxpro (1) are also mentioned in some of these reports. All of them are considered as **possible** adverse reactions to aluminium-containing vaccines.

Review of the non-serious ADR reports
Among the non-serious reports, several cases of granuloma or nodules (15) were described as well. Otherwise, mainly other known adverse reactions such as mild fever and redness at the injection site are described.

Conclusion
In the third quarter of 2014, we received a total of 60 reports that concerned vaccines in the childhood immunisation programme (excluding the HPV vaccine).

29 were classified as serious, and 22 of the reports described aluminium allergy and the formation of granuloma.

Granuloma were also described in many of the non-serious reports.

None of the new data shift the benefit-risk balance, and therefore the DHMA assesses that the benefits of the vaccine still outweigh the possible risks.

Reports about the HPV vaccine received in Q3 2014

In the third quarter of 2014, the DHMA received a total of 30 reports about the HPV vaccine, of which 14 were classified as serious.

Table 2a shows the number of ADR reports classified as serious and non-serious, respectively.

Vaccine	Serious	Non-serious	Total
HPV vaccine	14	16	30

Table 2a. Reports broken down by severity.

Number of doses sold and number of ADR reports from 2009-2014

HPV vaccine	2009	2010	2011	2012	2013	Until 30 September 2014	Total
Number of reports	288	66	43	96	511	155	1159
Number of serious reports	25	5	6	18	177	52	283
Number of doses sold	347,690	151,476	163,374	349,730	488,224	92,200	1,592,694

Table 2b. Number of ADR reports related to the HPV vaccine received from 2009 to 30 September 2014, broken down by serious and non-serious reports. The number of doses sold in Denmark is also shown. (Please be aware that when the DHMA receives additional information, this may imply changes. Consequently, there may be small variations between previously published figures and the figures reported here.)

Age distribution

The HPV vaccine is the only vaccine included in the Danish childhood immunisation programme that is also offered free of charge to women outside the childhood programme.

From August 2012 until end-2013, the HPV vaccine was offered free of charge to women from the 1985-1992 birth cohorts. Since 1 January 2014, the HPV vaccine has been offered to women from the 1993-1997 birth cohorts. These birth cohorts have previously been offered the HPV vaccine. The offer is available until the end of 2015.

Table 2c shows the age distribution of the girls/women described in the ADR reports we received in the third quarter.

Number of reports about persons under 18	Number of reports about persons aged 18 or over	Number of reports, age unknown
12	13	5

Table 2c. Age of the girls/women for whom adverse reactions have been reported

Review and assessment of the serious reports about the HPV vaccine (all Gardasil®)

ADR description	Assessment and causality
Bilateral papilledema, paresthesia, tinnitus (now in a habitual state)	The symptoms developed shortly after the vaccination course had been completed. Extensively examined. It is known from the literature that infection and other vaccines can cause the condition, which is why causality is considered **possible.**
Multiple symptoms with paresthesia, etc.	The patient has been diagnosed with post-traumatic stress syndrome, and causality is therefore considered **less likely.**
Epilepsy one month after vaccination	Epilepsy is a relatively common disorder. No link between epilepsy and the vaccine has been found in epidemiological studies, which is why causality is considered **less likely.**
Multiple symptoms with dizziness, etc.	Since there is no diagnosis and information is missing, it is **not possible to assess any causality.**
Multiple symptoms – POTS	In this particular case, the symptoms did not develop until one year after vaccination. It appears from the report that the patient had contracted Epstein-Barr virus, which provoked the symptoms. Therefore, it is considered **less likely** that the vaccine is what caused the symptoms.
POTS	The symptoms developed in connection with vaccination. Causality is considered **possible**
Multiple symptoms with pain and syncope over a longer period of time	These are symptoms resembling autonomic dysfunction, but there is no diagnosis. Given the present evidence, it is **not possible to assess whether there is a causal relationship**.
Multiple symptoms with pain, anxiety, etc.	The reported symptoms are non-specific. The patient also had another disease. Based on the information available, it is **not possible to assess any causality.**
Multiple sclerosis	The symptoms occurred three months after vaccination. As epidemiological studies do not indicate a connection between the vaccine and the disease, causality is considered **less likely**
Multiple sclerosis	The diagnosis concerns a women who already had the symptoms before vaccination, and since epidemiological studies do not indicate a connection between the vaccine and the disease, causality is considered **less likely**
Multiple symptoms with stomach ache, dizziness, etc.	The symptoms developed approx. three months after completion of the vaccine course. The patient has been examined, but a final diagnosis has yet to be made. Based on the information available, it is **not possible to assess any causality.**
Vaccinated with a seasonal influenza vaccine and Gardasil®: Subsequently had spontaneous abortion and developed multiple sclerosis.	Spontaneous abortion is relatively common in the general population. There is no evidence in the literature that the vaccine could provoke this. Multiple sclerosis was diagnosed more than two years after the last Gardasil® vaccine dose, and since epidemiological studies* have found no connection between the vaccine and the condition, causality is considered **less likely**

Congenital condition: myelomeningocele – skin-covered	The mother had completed the Gardasil® vaccine course approx. four months before pregnancy. There is no evidence in the literature indicating congenital effects of Gardasil®, not even when the vaccine is given in the beginning of pregnancy. In this case, the vaccine was given long before the pregnancy, and a causal relationship is therefore considered **less likely.**
Multiple symptoms with pain, tiredness, etc.	Despite several examinations, no diagnosis has been made. Based on the information available, it is **not possible to assess any causality**.

Table 2d. Description of the adverse reactions in the serious ADR reports and subsequent causality assessment.
*Arnheim-Dahlstrøm et al BMJ 2013.

Review of the non-serious ADR reports

The non-serious ADR reports represent a mix of symptoms, most of which related to the nervous system, e.g. headache, dizziness, fainting, etc. as well as local reactions at the injection site.

Conclusion

We received a total of 30 ADR reports that concerned the HPV vaccine in the third quarter of 2014. 14 of them were classified as serious.

The serious ADR reports have undergone our causality assessment. Causal relationships were assessed to exist in only a few of them. Some of the reports describe patients who developed epilepsy or multiple sclerosis suspected to be adverse reactions to HPV vaccination, but several epidemiological studies indicate no such causality.

The non-serious ADR reports mainly describe headache and dizziness.

None of the new data shift the benefit-risk balance, and therefore the DHMA assesses that the benefits of the HPV vaccine still outweigh the possible risks.

POTS and CRPS monitoring remains in focus

In early December, the Pharmacovigilance Risk Assessment Committee (PRAC) under the EU completed its routine annual review of Gardasil® safety. PRAC concluded that the vaccine's benefit-risk balance remains favourable. This means that the benefits of the HPV vaccine, which can prevent the development of cervical cancer, still outweigh the disadvantages associated with vaccination and the risks of adverse reactions.

In the December review of Gardasil® safety, the possible connection between the HPV vaccine and POTS[1] and CRPS[2] was thoroughly assessed. The PRAC concluded that presently it is not possible to confirm or disprove that there is a causal relationship between Gardasil® vaccination and the occurrence of POTS and CRPS, respectively. Therefore, POTS and CRPS should be monitored closely in future reviews of Gardasil® safety, and a special initiative in the form of a new questionnaire has been launched to ensure appropriate follow-up on ADR reports that describe symptoms suggestive of POTS or CRPS.

Worldwide, 66 reports have been registered describing POTS as a suspected adverse reaction after vaccination with the HPV vaccine[3]. The majority of these reports are from Denmark and the USA. Worldwide, the number of

[1] Postural Orthostatic Tachycardia Syndrome
[2] Complex regional pain syndrome.
[3] Figures are stated as at 30 September 2014.

reported CRPS cases is 47, one of which is from Denmark. Several conditions complicate the assessment of causality between the HPV vaccine and POTS and the HPV vaccine and CRPS. For example, POTS and CRPS are relatively new diagnoses that present with varied symptoms. In addition, POTS and CRPS are prevalent in the general population, the background rate in the general population is unknown and the causes of POTS and CRPS still remain unclear. In summary, it is difficult at present to assess whether there is a possible link between the HPV vaccine and POTS and CRPS, respectively. POTS and CRPS should therefore be monitored closely in future reviews of Gardasil® safety.

Reports of suspected adverse reactions related to influenza vaccine

The influenza season has begun, and the DHMA will therefore publish regular reports on suspected adverse reactions to the influenza vaccines in this season together with our assessment of the serious ADRs that are reported.

This season's vaccines
This season, people will be vaccinated with two vaccines (Fluarix and Vaxigrip) from two different manufacturers. Both vaccines contain components of inactivated influenza virus and are considered equal for protection against influenza.

Free influenza vaccination is offered to risk groups
As usual, the influenza season 2014/2015 starts on 1 October and the offer for free vaccination to risk groups[1] recommended by the DHMA enters into force.

Free vaccination must take place in the period from 1 October 2014 to the end of December 2014, however, before 1 March 2015 in respect of pregnant women and people with immunodeficiency and their household contacts.

ADR reports about the influenza vaccine in the period 1 August to 30 November 2014
In this report, we have analysed reports of possible adverse reactions to the influenza vaccine in the period from 1 August to 30 November 2014. There are 35 reports altogether.

Sales figures are not included in this report because the number of doses sold for the vaccines in question are not available before the beginning of 2015.

[1] The DHMA recommends that the following persons be vaccinated: Patients over 65 years of age who have a chronic disease, obese persons with a BMI over 40, pregnant women past 12 weeks of gestation. In addition, persons with immunodeficiency and their household contacts can be vaccinated free of charge. See the Danish executive order no. 962 of 27 August 2014 on free influenza vaccination to selected population groups.

Reports
In this period, the DHMA received a total of 35 ADR reports. Nine of them were classified as serious.

Review and assessment of the serious reports
When we assess the serious ADR reports, we investigate whether it is likely that the adverse reaction is connected to the vaccine.

The result of our causality assessment is split into three categories:

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

Vaccine	ADR description	Assessment and causality
Vaxigrip	Anaphylactic (shock) reaction	The event is described in limited terms, and it has not been possible to obtain further details. When the influenza vaccine is given, an anaphylactic reaction could occur, and causality is therefore considered **possible**.
Vaxigrip	A patient developed pain and reduced mobility of the left shoulder (frozen shoulder) in relation to vaccination. Ten months after vaccination, and despite physiotherapy, the patient still suffered reduced shoulder mobility.	Subsequent examinations revealed that the patient had periarthritis in the joint in question and tendinopathy of the left supraspinatus muscle. It is known from the literature that incorrect administration could cause shoulder injuries. Causality as regards periarthritis is therefore considered **possible.** Note, however, that it does not appear from the report that the administration was performed incorrectly and also that frozen shoulder is a common condition.

Vaxigrip	Two hours after vaccination, a patient felt unwell with severe nausea and vomiting. This continued for several days, and the patient was admitted to hospital due to dehydration. No examinations were made to detect other infectious agents.	The symptoms occurred immediately after the patient was vaccinated. General discomfort is a well-known adverse reaction to the vaccine. It is not described in the literature that nausea and vomiting after vaccination with Vaxigrip could be so severe that it could lead to dehydration. It is considered more likely that the symptoms of nausea and vomiting were caused by a gastroenteritis, which is common. Causality is therefore considered **less likely**.
Vaxigrip	A few days after vaccination, a patient presented with dyskinesia and chest pain, and one week after, the patient developed paresthesia of the feet. ECG and CAG showed that the patient did not have ischaemia. Weeks after the vaccination, the patient still had neurological symptoms and mild tightness of the chest.	There is a temporal relationship between the adverse reactions and vaccination, and there have been reports of neurological disturbances after the vaccine was marketed. Causality is considered **possible** as regards the neurological reactions. Chest pain has not previously been described as an adverse reaction to the vaccine.
Influenza vaccine[3] /Gardasil®	Three years ago, a citizen was vaccinated with Gardasil® and a seasonal influenza vaccine. Over these three years, the citizen has developed symptoms from many organ systems, including early menopause, reduced sexual urge, tiredness, headache, psychiatric symptoms such as anxiety and depression, muscle weakness, haemorrhoids, fluid bags under the eyes, loss of appetite, nettle rash, etc.	Some of the reported adverse reactions are known symptoms of the influenza vaccine, e.g. headache, loss of appetite and tiredness. Normally, these symptoms subside without treatment in a couple of days. After Gardasil® vaccination, it is also known that reactions such as temporary headache and nettle rash could occur. There is no evidence in the literature indicating that the influenza vaccine or the Gardasil® vaccine could cause such a syndrome as described in the report. Some of the reported symptoms could be caused by the menopause and the hormonal changes that follow. Causality is therefore considered **less likely**.

Table 1: Description of the adverse reactions in the serious ADR reports and subsequent causality assessment.

[3] It is not mentioned which vaccine was used.

Vaxigrip	In connection with vaccination, a patient experienced that existing atrial fibrillation was aggravated. This had happened before in connection with vaccination. Aggravation occurred about 24 hours after vaccination. The episodes were severe and lasted for 3-4 hours. In the four weeks after vaccination, the episodes were more frequent and severe than usual, but they subsided over time. At the time around vaccination, the patient developed a throat inflammation.	There is a temporal relationship between the episodes and vaccination, and it is assessed that the aggravated episodes may have been caused by the vaccination. It is therefore considered that the vaccination was a contributing factor to the aggravation and that causality is **possible**
Vaxigrip	On the same day of vaccination, a patient broke out in a rash across the body. The patient was treated with penicillin at the same time. IgE to penicillin subsequently turned out to be negative.	There is a temporal relationship between vaccination and the rash. Generalised skin reactions, covering itching, urticaria or non-specific rash, have previously been reported after marketing of the vaccine, and causality is therefore considered **possible.**
Vaxigrip	A few months after vaccination, a woman developed symptoms suggestive of multiple sclerosis.	Scientific articles disprove a connection between influenza vaccination and multiple sclerosis, which is why causality is considered **less likely.**
Fluarix	Three weeks after vaccination, a child developed erythema nodosum.	Erythema nodosum is a non-specific immunological reaction, most often idiopathic, but it is seen after e.g. streptococcal infections, Yersinia, TB and other infections and inflammatory intestinal conditions and medications. Erythema nodosum has been described as caused by other vaccines, but not after influenza vaccine. It cannot be ruled out entirely that the vaccine may provoke erythema nodosum, but since the literature has not established any evidence for a connection, causality is considered **less likely.**

Table 1: Description of the adverse reactions in the serious ADR reports and subsequent causality assessment.

Review of the non-serious ADR reports
The non-serious reports mainly describe cases of myalgia, arthralgia, fever, tiredness, dizziness, etc. arising in connection with vaccination. A considerable share also describe local reactions at the injection site. Most of these reactions are known adverse reactions to influenza vaccination, and they normally disappear without treatment in one to two days' time.

Conclusion
In the period from 1 August to 30 November 2014, the DHMA received a total of 35 reports of suspected adverse reactions to seasonal influenza vaccines. Nine of them were classified as serious.

The serious ADR reports described varying symptoms including anaphylactic shock, frozen shoulder, severe nausea and vomiting and paresthesia. The serious ADR reports have undergone our causality assessment, and in five cases we assessed it likely that they are related to the vaccine.

The non-serious reports mainly describe known adverse reactions such as arthralgia and myalgia.

The DHMA concludes that the benefits of the influenza vaccines still outweigh the possible risks.

Analysis of reported suspected adverse reactions and reported adverse events associated with using labour-stimulating medicines for induction of labour

Introduction

In August 2013 at the request of the Danish Ministry of Health, the DHMA prepared a *Plan for the monitoring and supervision of the Danish regions' use of labour-inducing medicines*. The main purpose of the plan is to increase the quality, safety and security of medically-induced labour. Among other things, the plan provides for the implementation in 2014-2016 of cross-cutting analyses of reported suspected adverse reactions and reported adverse events related to medically-induced labour.

The medicines used to induce labour are prostaglandins (misoprostol and dinoprostone) or synthetic pituitary hormone (oxytocin). Oxytocin is administered as an iv drip infusion primarily to induce labour after pre-labour rupture of the membranes, or to stimulate contractions when the woman is in labour. Prostaglandins can be taken orally or can be inserted as vaginal tablets.

Method

In this article, we provide the results from the first cross-cutting analyses of the reported suspected adverse reactions[1] and reported adverse events[2] registered in the DHMA's database of adverse reactions and the National Agency for Patients' Rights and Complaints' database of adverse events, the Danish Patient Safety Database (DPSD). Searches involve reports and adverse events related to dinoprostone, misoprostol and oxytocin received in 2013.

The analysis has been prepared jointly by the DHMA and the National Agency for Patients' Rights and Complaints.

[1] An adverse reaction to a medicinal product for human use is a response which is noxious and unintended, cf. the Danish executive order no. 381 of 9 April 2014 on the reporting of adverse reactions from medicines etc. (in Danish only).
[2] Adverse events include events and errors known in advance and unknown events and errors not caused by the patient's disease and which are either harmful or could have been harmful but which were prevented before occurring or which did not otherwise occur due to other circumstances, cf. the Danish executive order no. 1 of 3 January 2011 on reporting of adverse events in the health sector, etc. (in Danish only).

Results

A total of 30 birth processes have been identified for which suspected adverse reactions have been reported to the DHMA's adverse reaction database.

In the DPSD, a total of 37 adverse events have been identified in relation to birth processes. Some of these may be duplicates of the reported adverse reactions, however, to preserve anonymity in relation to the reports of adverse events, this can be neither confirmed or disproved.

The review of the individual reports of suspected adverse reactions and reported adverse events has identified the following five problem areas:

1. There are reports of suspected adverse reactions and adverse events involving the administration of misoprostol at higher doses than provided in the recommendations from the Danish Society of Obstetrics and Gynaecology[3].

2. There are reports of suspected adverse reactions describing rupture of the uterus and of adverse events describing hyperstimulation in women with previous caesarian section who, in connection with subsequent pregnancy, received labour-stimulating medicines for induction of labour.

3. There are reports of suspected adverse reactions and adverse events describing hyperstimulation of the uterus in women who were discharged temporarily after receiving misoprostol at the hospital.

4. There are reports of adverse events involving cases of incorrect oxytocin doses.

5. There are reports of adverse events describing problems with using the iv drip in connection with oxytocin administration.

Re 1) Administration of misoprostol at higher doses than recommended
Suspected adverse reactions and adverse events have been reported, including reports of hyperstimulation of the uterus and affected foetal heart sound after vaginal administration of misoprostol-containing medicines at doses higher than recommended. There are several reports about women who received 50ug vaginal misoprostol, which is higher than the recommended initial dose.

According to the current guideline for "Igangsættelse af fødsel (Induction of labour)"[4] prepared by the Danish Society of Obstetrics and Gynaecology (DSOG), the recommended regime for vaginal misoprostol is 25ug every four hours. Misoprostol is administered at least two times and not more than four times within 24 hours before birth.

The recommended regime for vaginal misoprostol should not be mixed up with the regime for oral misoprostol, which, under normal circumstances, is given in doses of 50ug every four hours and not more than four times in every 24 hours.

Re 2) Induction of labour in women with previous caesarian sections
Reports of suspected adverse reactions have been submitted describing women with previous caesarian sections who had rupture of the uterus after administration of dinoprostone followed by oxytocin to induce labour in subsequent pregnancy. Other reports described hyperstimulation without rupture of the uterus.

[3] Igangsættelse af fødsel (2013) – Danish guideline about induction of labour. DSOG Sandbjerg Guideline
[4] Igangsættelse af fødsel (2013) – Danish guideline about induction of labour. DSOG Sandbjerg Guideline

In this group, there were also reports of adverse events where labour had been induced with misoprostol even though the below guideline provides that it must not be used.

According to the guideline for "Sectio antea"[5] prepared by DSOG, women with previous non-classical caesarean sections, i.e. a lower transverse caesarean section, are offered oxytocin for induction of labour after pre-labour rupture of the membranes under close observation in the ward. Induction of labour with dinoprostone is recommended only in special circumstances and under close monitoring.

Re 3) Temporary discharge after administration of misoprostol in hospital
Suspected adverse reactions and adverse events have been reported describing women who after administration of misoprostol were discharged temporarily and subsequently experienced hyperstimulation of the uterus at home.

Re 4) Incorrect oxytocin doses
The reported adverse events describe several errors arising when diluting oxytocin in saline as well as errors in connection with programming the pump infusion rates, which implied that the women received too much oxytocin and thus experienced hyperstimulation of the uterus. In several of the events, it is described that the regions have sent out new guidelines about the dilution ratio and infusion rates contributing to confusion. Reference is made to the summary of product characteristics for Syntocinon®, which thoroughly describes the dosage regime and administration method.

Re 5) Problems with the oxytocin iv drip
In several of the reports about adverse events, it is described that there are problems with using the infusion device in connection with oxytocin administration. These problems are general and relate to user errors when operating the medical device and thus do not concern oxytocin specifically. For example, there are several events where oxytocin and saline were given in parallel, and oxytocin flowed into the saline bag.

An adverse event also described a hose clamp, which by mistake had not be closed, the result being that the woman experienced hyperstimulation of the uterus. Another adverse event described a scenario where the drip tube was not inserted properly into the infusion pump, the result being that oxytocin was infused too quickly into the pregnant woman.

Discussion and conclusion

Different types of adverse events and suspected adverse reactions have been reported in the use of labour-stimulating medicines for induction of labour. They especially address hyperstimulation of the uterus caused by the administration of vaginal misoprostol at higher doses than recommended. Hyperstimulation of the uterus was also described in cases where women had been discharged temporarily. We also saw reports about pregnant women who had previously delivered by caesarean section who experienced hyperstimulation of the uterus or had rupture of the uterus after medically-induced labour.

The reported adverse events also concerned problems of diluting the medicine correctly and problems with operating the device for administration of the medicine.

The DHMA maintains that the benefits of using labour-stimulating medicines for induction of labour outweigh the possible risks. Pursuant to the "Plan for the monitoring and supervision of the Danish regions' use of labour-inducing medicines", the DHMA will continue its work to monitor and supervise the regions' use of labour-inducing medicines in close collaboration with all stakeholders involved, including the Danish Regions, DSOG, the Danish Association of Midwives, Statens Serum Institut, National Institute for Health Data and Disease Control (SSI) and the National Agency for Patients' Rights and Complaints.

[5] Sectio antea (2013) – Danish guideline DSOG Sandbjerg Guideline

Antihistamine promethazine (Phenergan® etc.) now available by prescription only

Following a recent review of the safety of using promethazine in disorders including allergic diseases, motion sickness and insomnia, the DHMA has changed the medicine's status from over-the-counter to prescription-only. The prescription-only status applies to both Phenergan®/Prometazin ERA 25 mg film-coated tablets in units of 100 and Phenergan® 1 mg/ml oral solution for children from two years of age. The prescription-only status became effective on 8 December 2014.

Following a period of increasing concern about promethazine's potential for abuse, this has now been confirmed in practice.

Increased focus on promethazine safety after a report form a proprietary pharmacist
It was a report from a proprietary pharmacist that prompted us to put focus on the use of promethazine. In *Danish Pharmacovigilance Update, December 2012*, we reported that we were monitoring promethazine closely and encouraged the reporting of any suspicion about excessive use or abuse of drugs. We subsequently received a new report about suspected promethazine abuse, and we were concurrently informed that the Danish Poison Control Hotline had received several calls about inappropriate use of promethazine. The DHMA therefore joint forces with the Danish Poison Control Hotline to identify potential safety problems associated with promethazine.

Grounds leading to promethazine's prescription-only status

We identified four serious safety problems associated with using Phenergan® and Prometazin ERA 25 mg film-coated tablets in units of 100:

1. Abuse of higher doses than recommended
2. Serious adverse reactions at recommended doses
3. Serious interactions with psychoactive drugs
4. Heavy sedative effect compromising the ability to drive

Re 1) Abuse of higher doses than recommended
Within a period of seven years (2006-2012), sales of promethazine has more than doubled, over-the-counter sales accounting for two thirds of total sales. During this period, the Danish Poison Control Hotline received 212 calls about overdoses with Phenergan® and Prometazin ERA. Whereas 25 of these calls concerned medicine abuse, 182 of the calls were about suicide attempts[1]. The number of calls made to the Danish Poison Control Hotline about promethazine has exploded in the past couple of years – from two calls in 2006 (August to December) and 14 in 2007 to 170 calls in 2014 (January to September).

Re 2) Serious adverse reactions at recommended doses
Serious adverse reactions could occur when using promethazine. Both the medicine's summary of product characteristics and the literature describe cases of serious adverse reactions after using promethazine at recommended doses. Adverse reactions in the summary of product characteristics for Phenergan® include extrapyramidal effects, muscle spasms and tic-like movements of the head and face[2]. The literature also describes neuroleptic malignant syndrome[3]. It is therefore important that doctors remain alert to the early symptoms of serious adverse reactions and immediately discontinue promethazine and any other dopamine antagonists.

[1] Dalhoff K, Askener G. Promethazine used as a recreational drug in Denmark. Basic & Clinical 115, Issue Supplement s1, Article first published online: 23 June 2014
[2] The DHMA's summary of product characteristics for Phenergan, 25 mg film-coated tablets of 8 December 2014 (in Danish).
[3] Chan-Tack KM. Neuroleptic malignant syndrome due to promethazine. South Med J. Oct: 92 (10): 1017-8

Re 3) Serious interactions with psychoactive drugs
Promethazine interacts with several types of psychoactive drugs. It may enhance the sedative effect of anxiolytics, antipsychotics, hypnotics and alcohol, increase the cardiotoxicity of MAO inhibitors as well as enhance the anticholinergic effects of cyclic antidepressants and decrease the effect of cholinesterase inhibitors. In addition, MAO inhibitors may enhance the anticholinergic adverse effects of promethazine for up to 14 days after treatment has been discontinued[4]. Several of the calls made to the Danish Poison Control Hotline about overdoses, concerned individuals who were treated concomitantly with another medicine – predominantly benzodiazepines – but also antipsychotics and antidepressants.

Continued use of the medicine at therapeutic doses without the advice from a doctor is problematic, not only because of the risk of abuse, but because of the medicine's potential interactions with other psychoactive drugs.

According to the summary of product characteristics, the medicine also has the potential of aggravating symptoms in patients with sleep apnoea, asthma, bronchitis or bronchiectasis because the medicine may thicken or dry lung secretions and impair expectoration, which is why it should be used with caution in these patients. Likewise the medicine should only be used cautiously in epileptic patients[4].

Re 4) Heavy sedative effect compromising the ability to drive
Promethazine has a half-life of 5-14 hours[4]. Due to promethazine's heavy sedative effect and long half-life, patients should be advised by a doctor about driving a motor vehicle before initiating treatment with promethazine.

The latest review by the Institute for Rational Pharmacotherapy (IRF) of medicines affecting the ability to drive provides that the sedative effect of antihistamines varies between products and that the effect on cognitive functions varies from patient to patient – e.g. promethazine is a heavy sedative, and patients taking it should be prohibited from driving. Read the IRF's review here (in Danish only): *Trafik og lægemidler (Drugs and driving)*

Phenergan® 1 mg/ml oral solution for children from two years of age and risk of serious adverse reactions at recommended doses

In Denmark, promethazine is contraindicated in children younger than two years of age due to the risk of fatal respiratory depression[5]. The US summary of product characteristics provides that caution should be exercised when administering Phenergan® due to the potential for fatal respiratory depression also in children older than two years of age. This is also seen when the medicine is taken together with other medicines with respiratory depressant effects[6].

According to a study, most children who receive the recommended doses will have adverse reactions. The most common reactions are sedation and inability to focus. Hallucinations, convulsions and encephalopathy have also been seen at recommended doses[7]. In children, especially feverish children, extrapyramidal effects were seen. Acute dystonic reactions have been described, which may be painful if left untreated, and fatal if affecting the laryngeal muscles[8,9]. Due to the medicine's risk profile, it should be prescribed by the doctor.

Reports in Denmark about Phenergan® 1 mg/ml oral solution for children from two years of age
In the Danish database of adverse reactions, one case has been reported describing a two-year-old presenting with adverse reactions such as crying, nervousness, nosebleed, abnormal breathing and snoring as well as fear after having taken the medicine.

[4] The DHMA's summary of product characteristics for Phenergan, 25 mg film-coated tablets of 8 December 2014 (in Danish).
[5] The DHMA's summary of product characteristics for Phenergan oral solution of 8 December 2014 (in Danish).
[6] http://www.accessdata.fda.gov/drugsatfda_docs/label/2004/07935s030lbl.pdf
[7] Hickson GB, Altemeier WA, Clayton E. Should Promethazine in Liquid Form Be Available Without Prescription? +45 1990 86 221 -5
[8] DeGrandi T, Simon JE. Promethazine-induced dystonic reaction. Pedatri Emerg Care. 1987 Jun: 3(2): 91-2
[9] Darwish H, Grant R, Haslem R, Roth S. Promethazine-induced acute dystonic reactions. Am J Dis Child, 1980 Oct: 134(10): 990-1

Calls to the Danish Poison Control Hotline about Phenergan® 1 mg/ml oral solution for children from two years of age
The Danish Poison Control Hotline has received five calls in total about children who had received Phenergan® 1 mg/ml oral solution. Two calls concerned serious overdoses due to incorrect administration in connection with playing or mix-up with another medicine. Two other calls concerned unintended overdoses where children were given respectively 0.64 mg/kg and 3 mg/kg.

The last call concerned a 13-year-old girl who had attempted suicide.

Promethazine is an older sedative antihistamine marketed for the first time in 1955.

Promethazine is indicated for:

- Allergic diseases, especially urticaria
- Hay fever and allergic rhinitis
- Motion sickness and insomnia (only authorised for insomnia in adults)

In Denmark, Phenergan® is contraindicated in children younger than two years of age due to the risk of fatal respiratory depression.

In Sweden, Norway, Germany and the Netherlands, it has been a prescription medicine since marketing. In Sweden and Germany, the medicine is also used to treat certain psychiatric disorders.

Pantoprazole (Pantoloc® etc.) and vitamin B12 deficiency

In October, the DHMA received an ADR report concerning a patient who developed vitamin B12 deficiency while being treated with pantoprazole.

The patient, who had been treated with pantoprazole for gastroesophageal reflux disease, consulted his/her own specialist about uncharacteristic symptoms including periodic dizziness. Examinations revealed vitamin B12 deficiency. The patient did not have anaemia.

The patient continued using pantoprazole only when needed and started oral treatment with vitamin B12, however, the symptoms continued. Pantoprazole was stopped completely, and the patient was hospitalised for further treatment. The patient was examined, and no other causes were found that could explain the inability to absorb vitamin B12.

After pantoprazole was discontinued, serum B12 levels normalised.

The DHMA has received no other reports describing vitamin B12 deficiency related to pantoprazole treatment.

Doctors should be aware of the following:

- Pantoprazole, as all acid-blocking medicines, may reduce the absorption of cyanocobalamin due to hypo- or achlorhydria.
- This should be considered for patients with reduced cyanocobalamin stores (low plasma cobalamins) or other risk factors for reduced cyanocobalamin absorption on long-term therapy or if respective clinical symptoms are observed (symptoms of anaemia).

Indication for Pantoloc® 40mg

Adults and adolescents 12 years of age and above:

- Reflux oesophagitis

Adults:

- Eradication of Helicobacter pylori (H. pylori) in combination with two appropriate antibiotics in patients with H. pylori associated ulcers.
- Gastric and duodenal ulcer
- Zollinger-Ellison Syndrome and other pathological hypersecretory conditions

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:

- **Mycophenolate mofetil immunosuppressant (CellCept):** New warnings about the risk of hypogammaglobulinemia and bronchiectasis.
- **Immunosuppressant dimethyl fumarate (Tecfidera):** Progressive multifocal leukoencephalopathy (PML) has occurred in a patient with severe and prolonged lymphopenia.
- **Regadenoson (Rapiscan) for radionuclide myocardial perfusion imaging:** New important advice to minimise the risk of cerebrovascular accident and the risk of prolongation of Raptiscan-induced seizures following administration of aminophylline.
- **Ivabradine (Procoralan) for angina pectoris and heart failure:** New contraindication and recommendations to minimise the risk of cardiovascular events and severe bradycardia. **Also see the article in** *Danish Pharmacovigilance Update, November 2014.*

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

Adverse events and suspected adverse reactions related to insulin therapy

The National Agency for Patients' Rights and Complaints has just published a thematic report about adverse events related to insulin therapy. The DHMA has contributed to the report and investigated reports of suspected adverse reactions related to insulin therapy. The report is in Danish and available here: *Behandling med insulin – identifikation af utilsigtede hændelser og forslag til forebyggende tiltag (Insulin therapy – identification of adverse events and proposals for preventive measures)*.

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