Danish Pharmacovigilance Update # 1

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Chlorhexidine may cause skin damage to newborn babies

The European Medicines Agency, EMA, has reviewed reports of chemical skin injuries in newborn babies, including burns in premature infants when chlorhexidine solutions are used for skin disinfection.

Efficient skin disinfection is crucial in premature infants because their risk of infections is high and because they often require procedures that in itself increase the risk of infection.

Healthcare professionals should pay special attention to the risk of chemical skin burns and take adequate precautionary measures.

Advice to healthcare professionals:

- There is a risk of chemical injuries when using alcohol-based or water-based chlorhexidine solutions in newborns.
- The risk is highest for those born before 32 weeks of gestation and within the first 2 weeks of life.
- Make sure the solution does not pool underneath the newborn, in the newborn's skin folds or spills on materials that are in direct contact with the newborn's skin.
- Be alert, and handle any skin damage as quickly as possible.

No solutions with chlorhexidine are authorised as medicinal products in Denmark.

Since this is not a medicinal product, any adverse reactions arising from the use of chlorhexidine solutions are not reported to the DHMA.

The Danish Patient Safety Database has received a few individual reports of adverse events concerning chemical skin injuries in patients exposed to chlorhexidine solutions.

Small risk of severe allergic reactions to ambroxol and bromhexine (Flavamed® etc.)

The European Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review of medicines containing ambroxol and bromhexine. The review included available data about ambroxol and bromhexine, which is converted into ambroxol in the body, and all reports of severe allergic reactions and skin reactions associated with these medicines.

The PRAC concluded that the known risk of allergic reactions was confirmed, however, that it is still assessed to be small. Among the allergic reactions were severe skin reactions such as erythema multiforme and Stevens-Johnson syndrome.

Doctors should be aware of the following:

- Treatment with ambroxol and bromhexine should be discontinued if severe skin reactions occur.
- Patients should be informed of symptoms suggestive of severe allergic reactions and advised to stop treatment immediately and consult their doctor if they develop these symptoms.

The product information will be updated
The PRAC recommends that the summaries of product characteristics for ambroxol- and bromhexine-containing medicines be updated with the risk of severe skin reactions as well as the risk of severe allergic reactions and advice to discontinue treatment immediately if these symptoms occur.

Indication for ambroxol and bromhexine:
Used as an expectorant/mucolytic to decrease secretion viscosity to help clear mucus from the airways.

Ambroxol- and bromhexine-containing products are marketed as single products and in combination with other active ingredients. They are also available over the counter.

Read the press release at the website of the European Medicines Agency: *PRAC considers risk of severe allergic reactions with ambroxol- and bromhexine-containing medicines to be small*

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 signal discussed on the PRAC meeting in December 2014 concerns the following product:

- **Vildagliptin: Vildagliptin/metformin** – Myalgia

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.

Atorvastatin and hepatitis

In October 2014, the DHMA received an ADR report about an elderly man who developed hepatitis after being treated with atorvastatin for just under a month.

The medicine was discontinued, and the patient recovered in a couple of weeks.

Doctors should be aware of the following:

- The risk of liver effects are described for all statins.
- Atorvastatin is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.
- Liver function tests should be performed before the initiation of treatment and periodically thereafter. Patients who develop any signs or symptoms suggestive of liver injury should have liver function tests performed. Patients who develop increased transaminase levels should be monitored until the abnormality(ies) resolve. Should an increase in transaminases greater than 3 times the upper limit of normal persist, reduction of dose or withdrawal of the medicine is recommended.
- Statins should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease.

The DHMA has received altogether 36 ADR reports that describe liver effects related to treatment with atorvastatin.

In 2013, there were 119,778 persons who redeemed prescriptions for atorvastatin[1].

Indications for atorvastatin:

Hypercholesterolemia

Prevention of cardiovascular events in adults who have a high risk for a first cardiovascular event as an adjunct to correction of other risk factors.

[1]Kilde: Medstat

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:

- **Epileptic medicine valproate (Deprakine etc.):** Risk of congenital malformations
  See article in *Danish Pharmacovigilance Update, October 2014.*

- **Nitric oxide in cylinders for the treatment of pulmonary hypertension (INOmax (medical device)):** valve defect might stop gas delivery early in some cylinders.

The DHPCs are available in Danish at the DHMA website: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals.*

New report from the DHMA on monitoring the safety of medicines used off-label in Denmark

In the last few years, there has been increased focus on monitoring the safety of medicines used off-label. Both the DHMA and the rest of the EU have raised awareness on the use of medicines for treatments that are not covered by the medicine's authorised summary of product characteristics and the need for improving safety monitoring in off-labe use.

In a new Danish report, the DHMA puts focus on the work with *Monitoring the safety of medicines used off-label in Denmark (Danish title: Overvågning af sikkerheden ved off label-brug af medicin i Danmark).*

Classification of causality assessments

Background

The DHMA's medicines safety monitoring takes place in international settings.

At the DHMA, we collaborate with the WHO, the drug regulatory authorities in the other EU member states and the European Medicines Agency (EMA) on the monitoring of drug safety. We send reports of suspected adverse reactions to the common European adverse reaction database held by the EMA and to the WHO.

ADR signals are analysed and compared to data held in e.g. the European adverse reaction database, scientific studies and periodic safety update reports. In many cases, ADR signals are discussed in the EU's Pharmacovigilance Risk Assessment Committee, PRAC, in order to assess if certain medicines show signs of new or changed risks and whether precautionary measures or further investigation are required.

Short news

The WHO has published a new classification of causality assessment for reports of suspected adverse reactions to vaccines[1].

This classification includes an extra category compared to the previously used classification. The DHMA wants to adopt the new classification, which is international, as it may strengthen pharmacovigilance and provide a better basis for exchanging ADR data with other countries. For this reason, we have changed the classification as at 1 January 2015.

Causality assessment

The DHMA routinely assesses causality for reports of suspected adverse reactions to vaccines included in the childhood immunisation programme.

When we assess causality for a reported suspected adverse reaction, we take a number of factors into account, including if there is a temporal association between symptom onset and vaccination, if the vaccinees' have other diseases that could explain the symptoms, if other medicines have been given that could explain the symptoms, and if it has already been documented that the vaccine could cause the reported type of adverse reaction.

The previous classification

Before, we used a three-grade classification to assess causality:

- Possible
- Less likely
- Not possible to assess

The new classification

The new classification has four categories:

- Possible
- Insufficient documentation
- Less likely
- Unclassifiable (not possible to assess because of inadequate information)

The new category is "Insufficient documentation". This category contains the reports for which it was not possible to determine whether or not there is a possible connection between the reaction and the vaccine because of insufficient documentation. Reports in this category concern symptoms occurring in temporal association with vaccination, where the vaccinees' have no other immediate factors that may explain the symptoms (other disease, other medicine, etc.), but where there is no evidence in the literature or other available data that can confirm a causal relationship.

[1]Causality assessment of an adverse event following immunization (2013) (www.who.int/vaccine_safety)

Short news

Categories

The additional category "Insufficient documentation" may strengthen our monitoring activities because we get even better possibilities for quicker identification of reports of suspected adverse reactions that require special attention in our measures ahead.

The four categories.

Possible

1. Consistent temporal relationship between vaccination and symptoms, and there is documentation for the occurrence of the reported type of adverse reaction after vaccination.
2. Adverse events*
3. Reaction caused by vaccine quality defect **
4. Anxiety reaction caused by vaccination ***

Insufficient documentation

1. Consistent temporal relationship between vaccination and symptoms, but there is no or indeterminate documentation for the occurrence of the reported type of adverse reaction after vaccination.
2. Data are conflicting

Less likely

Other known disease or other factors are more likely to explain the symptoms.

Unclassifiable

The information in the report is inadequate, and it cannot be assessed if the symptoms are related to the vaccine ****

Conclusion

The DHMA believes that changing the classification of causality assessment will strengthen national as well as international efforts.

With this new classification, those ADR reports where a possible connection is indeterminable because of insufficient documentation are separated from the other reports in a category of their own, allowing the DHMA to put more focus on these reports. It gives us even better opportunities for quicker identification of reports of suspected adverse reactions that require special attention in our activities ahead.

When we use an international classification, the DHMA also builds a better basis for exchanging ADR data with the WHO and the EMA, which will strengthen international collaboration.

*Adverse events occurring in connection with subscription, dose and vaccine administration.

**Symptoms related to vaccine quality problems (batch defect, durability).

***Anxiety reactions could for example be fainting in connection with vaccination.

****When ADR reports are unclassifiable, the DHMA attempts to obtain further information to enable causality assessment.

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