Aspects of Pharmacovigilance in Neonates

Paul-Ehrlich-Institut
Dirk Mentzer
Paul-Ehrlich-Str. 51-59
63225 Langen

arzneimittelsicherheit@pei.de
http://www.pei.de
Aspects of Pharmacovigilance in Neonates

Points to consider

- Guidelines
- Challenge
- Target population
- Pharmacovigilance tools
- Present situation
- Further development

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

EU - legislation and Guidelines

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Guidelines (ICH, CHMP)

• Guideline on conducting trial in small population
• Guideline on Pharmacovigilance in Paediatric population
• Guideline on Risk Management Plan and Pharmacovigilance Plan
• Guideline on the Need for Pre-clinical Testing of Human Pharmaceuticals in Juvenile Animals
• Clinical Investigation of Medicinal Products in the Paediatric Population (ICH E11)
• draft guidelines many more to come with respect to neonates
Aspects of Pharmacovigilance in Neonates

Target population
Aspects of Pharmacovigilance in Neonates

Target population

• Neonate periode is covering the age range 0 - 28 days post delivery.

• The neonate may be differentiated into
  • preterm (before 37 weeks gestation)
  • term infant (from 37 – 42 weeks gestation)
  • Post term (after 42 weeks gestation)

• Approximately 50 - 90% of drugs used for treatment in the paediatric population are not authorised

• Usage of those drugs is mainly related to neonatal intensive care treatment, approximately 3 – 5% of all newborn will tent to be multi drug users
Aspects of Pharmacovigilance in Neonates

Target population

• perinatal complication
  • meconium aspiration, metabolic disease, respiratory adaptation problems, infection, nutrition

• Congenital disease/ malformation
  • CNS, heart malformation, intestinal- or intrathoracic (diaphragmatic hernia, malrotation), coagulation, haematological

• acquired Disease
  • Coagulation, metabolic, infection, respiratory
### Aspects of Pharmacovigilance in Neonates

<table>
<thead>
<tr>
<th>Target population</th>
<th>Neonates</th>
<th>≠</th>
<th>Rarely problems with drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates =&gt; Indication and dosage</td>
<td></td>
<td>=&gt;</td>
<td>Indication and dosage</td>
</tr>
<tr>
<td>Neonates =&gt; appropriate formulation</td>
<td></td>
<td>=&gt;</td>
<td>appropriate formulation</td>
</tr>
<tr>
<td>Neonates =&gt; Organ impairment</td>
<td></td>
<td>=&gt;</td>
<td>Organ impairment</td>
</tr>
<tr>
<td>Neonates =&gt; small numbers to be treated</td>
<td></td>
<td>=&gt;</td>
<td>small numbers to be treated</td>
</tr>
<tr>
<td>Neonates =&gt; Multifactorial Pharmacovigilance</td>
<td></td>
<td>=&gt;</td>
<td>Multifactorial Pharmacovigilance</td>
</tr>
</tbody>
</table>
# Aspects of Pharmacovigilance in Neonates

<table>
<thead>
<tr>
<th>Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>• trials enrolling several hundred patients may not be practical or possible in most cases and even common adverse reaction may not be detectable.</td>
</tr>
<tr>
<td>• In particular, if there is a latent period before onset or a trigger such as a change in growth, maturation or development.</td>
</tr>
<tr>
<td>• Conducting, analysis, and interpretation of studies within the neonatal population may at times be constrained by the prevalence of the disease and varying degrees (e.g. neurometabolic disease)</td>
</tr>
<tr>
<td>• increased effort to conduct pharmacovigilance in pre and post authorisation period</td>
</tr>
</tbody>
</table>

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Challenge

• Long-term follow up is important for designated treatment and is essential for capturing effects on skeletal, neural, behavioural, sexual and immune maturation and development.

• Pathophysiological knowledge of organ function supported by juvenile animal toxicology studies, mutagenicity and carcinogenicity data.

• Assessing a risk management plan (RMP) and Pharmacovigilance Plan (PP) in view of proposed indication or usage in the neonate population.

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Challenge

• The benefit/ risk assessment may be significantly different depending on the indication for which the product is used and may be influenced by the availability of other therapeutic options available.

• Long-term benefit/ risk may be in contradiction to the benefit/ risk assessment at time of drug administration

• Extrapolation of experience from Adult to neonates is not feasible with respect to different indication

• Monitoring ADRs with laboratory values may be very difficult due to lack of normal ranges information

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Pharmacovigilance tools
Aspects of Pharmacovigilance in Neonates

Pharmacovigilance tools

- Well-planned use of best available techniques to obtain and analyse information in the post-marketing phase is crucial. => case definition

- The observation and monitoring of the patient should contribute as much information as possible to support the Pharmacovigilance assessment at any time. => consumer reports, enhanced reporting

- Detailed knowledge of the pathophysiology of the disease and the pharmacology of the drug gained from the preauthorisation is essential for the causality assessment. => training and education of doctors

- Non-clinical pharmacology studies may are of special importance for assessment of ADRs => juvenile animal studies, pathomechanism

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

- Well-planned use of best available techniques to obtain and analyse information in the post-marketing phase is crucial. => case definition

- The observation and monitoring of the patient should contribute as much information as possible to support the Pharmacovigilance assessment at any time. => consumer reports, enhanced reporting

- Detailed knowledge of the pathophysiology of the disease and the pharmacology of the drug gained from the preauthorisation is essential for the causality assessment. => training and education of doctors

- Non-clinical pharmacology studies may are of special importance for assessment of ADRs => juvenile animal studies, pathomechanism
Aspects of Pharmacovigilance in Neonates

Pharmacovigilance tools

- **case definition**
  - data collection
  - data analysis
  - data presentation, assessment

- **enhanced reporting**
  - intensified monitoring at bed-side
  - Biomarker, surrogate markers

- **pathomechanism**
  - in vitro studies
  - animal studies/ juvenile animal toxicology studies

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Pharmacovigilance tools

• case definition
  - data collection => monitoring, clinical documentation
  - data analysis => normal values, scoring system
  - data presentation, assessment => publication, training

• enhanced reporting
  - intensified monitoring at bed-side => human resources
  - Biomarker, surrogate markers => appropriateness

• pathomechanism
  - in vitro studies => supporting non profitable research
  - animal studies/ juvenile animal toxicology studies
Aspects of Pharmacovigilance in Neonates

Present situation in Pharmacovigilance

• Case reports of adverse drug reactions are particularly useful to detect potential associations between specific medicines and adverse events.

• The assessment of causality is more difficult when
  1. there is a longer time lag between drug use and AE
  2. there is input on secondary effects like maturation

• To establish a causal association, further research is necessary using cohort, case-control studies or randomized trials

• Randomized trials may be preferred from a methodological point, but are not always useful and practical in rare disease.

• Defining age-, gender- and calendar period specific risks from population-based disease registries for comparison.

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Present situation in Pharmacovigilance

Patient registries - treatment registries

- important information on the natural course of disease
- help in the assessment of effectiveness and safety
- serve as a source for historical controls
- should meet high data quality standards
- not available in every EU-member state (data protection)

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Further development

Pharmacovigilance

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Further development

Risk Communication

Identified and potential Risks

Enhanced reporting and education

Surveillance and controlled trials

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Further development

Risk Communication
- Rapid-Alert-System (NUI), DHCP,
- Warning SPC, PSUR

Identified and potential Risks

Enhanced reporting and education

Surveillance and controlled trials
Aspects of Pharmacovigilance in Neonates

Risk Communication

Pubic

MS

Eudrovigilance/ Eudranet

RAS/ NUI

USR

EMEA

CHMP

DHCP/ DDL?

Suspension

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Further development

Risk Communication
- Rapid-Alert-System (NUI), DHCP,
- Warning SPC, PSUR

Identified and potential Risks
- registries, signal detection, in vitro studies
- research in pharmacovigilance

Enhanced reporting and education

Surveillance and controlled trials

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Identified and potential risks

- The incidence of adverse drug reactions in Off-label drug use is significantly associated with adverse drug reactions

- particularly when the drug was due to an indication different than that defined in the Summary Product Characteristics.

- Support of non-profitable research and research conducted by learned societies

- Post natal data collection to be linked with long-term follow up regarding late onset ADRs like growth, maturation (mentally and physically)
Aspects of Pharmacovigilance in Neonates

Further development

Risk Communication
- Rapid-Alert-System (NUI), DHCP,
- Warning SPC, PSUR

Identified and potential Risks
- registries, signal detection, in vitro studies
- research in pharmacovigilance

Enhanced reporting and education
- consumer (parents) reports
- simplified reporting via web-tool

Surveillance and controlled trials

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Enhanced reporting and Education

- The mechanisms for detecting new safety signals like spontaneous reporting systems have to include the consumer (=> parents).

- The marketing authorisation holder and the regulatory authorities have to take appropriate measures to provide sufficient educational information (readability of SPC)

- Proactive approach is needed like: specialist networks, clinical pharmacologist in Paediatrics, disease and treatment databases and active surveillance and clinical trials networks (national and international)
Aspects of Pharmacovigilance in Neonates

Further development

Risk Communication
- Rapid-Alert-System (NUI), DHCP,
- Warning SPC, PSUR

Identified and potential Risks
- registries, signal detection, in vitro studies
- research in pharmacovigilance

Enhanced reporting and education
- consumer (parents) reports
- simplified reporting via web-tool

Surveillance and controlled trials
- Signal detection tools, Epidemiological studies
- Post-marketing safety studies/ surveillance

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Surveillance and controlled trials

• Signal detection tools
  
  Searching case report in a databases with the Proportional Reporting Ratio with an appropriate stratification of data in the data warehouse which needs to be established

• Epidemiological studies using patient database
  
  Provides information regarding the natural incidence of a specific event in the general population

• Post-Marketing safety surveillance
  
  Ideally estimates of the incidence of adverse reactions in the target population and provides a causal relationship between drug and adverse event and risk factors predisposing to specific adverse events.

Dirk Mentzer, Neonate Workshop EMEA, October 2006
Aspects of Pharmacovigilance in Neonates

Thank you for your attention!

The smallest should give the direction.

Dirk Mentzer, Neonate Workshop EMEA, October 2006