Pharmacovigilance in Paediatric Population

The PRAC’s perspective

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Chair, PRAC

EMA Workshop
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Outline of presentation

• What is **PRAC’s experience** to date of pharmacovigilance in the paediatric population?

• What do we consider are **special challenges** in paediatric pharmacovigilance?

• What are the **new EU legislative tools** which can strengthen paediatric pharmacovigilance?

• What are the **current opportunities and priorities for** paediatric pharmacovigilance?
Pharmacovigilance Risk Assessment Committee

All aspects of the risk management of the use of medicinal products including the detection, assessment, minimisation and communication relating to the risk of adverse reactions, having due regard to the therapeutic effect of the medicinal product, the design and evaluation of post-authorisation safety studies and pharmacovigilance audit.
Pharmacovigilance cycle

Gaining knowledge of risks & risk management in therapeutic use
PRAC’s three public health pillars

Proactive safety monitoring & planning

Prompt benefit risk action

Transparency and communication
PRAC’s legislative tools ...

- New safety signals
- **Urgent and non urgent union procedures** triggered due to safety concerns identified in medicinal product(s) authorised in more than one member state
- **Risk Management Plans**
- Non-interventional safety study protocols and study reports if the need for a **non-interventional post-authorisation safety study** is identified
- **Periodic Safety Update Reports**
- List of **medicines under additional monitoring**
% of PRAC plenary discussion time 2013, based on total hours

- Referrals: 33%
- RMPs: 19%
- PSURs: 16%
- PASSs: 4%
- Renewals: 4%
- Other: 14%
- Signals: 10%
What are PRAC’s achievements in first 18 months?

- **Proactive pharmacovigilance**
  756 RMPs (160 products), 202 PASS studies registered

- **Real-time signal detection & prioritisation**
  - 121 signals, leading to 57 label updates

- **Additional monitoring scheme** in place

- **Prompt action on benefit risk issues** - recommendations on 486 PSURs, 22 referrals started, 13 completed in average time of 6.4 months

- **New era for transparency** in EU drug safety systems - agenda, highlights, full committee minutes published
And for the paediatric population?

- The first Article 31 referral and first article 107i referral
- Thirteen signals
- Risk management plans – vaccines in particular
- PASS – the first to include efficacy outcomes?
- Communications – on referral outcomes

A relatively small but important and challenging proportion of PRAC’s work
Referrals relating to medicines used in the paediatric population

- **Codeine** for analgesia and opiate toxicity in CYP2D6 ultra-rapid metabolisers
- **Numeta** for parenteral nutrition and reports of hypermagnesaemia
- **Octocog alfa** and inhibitor antibodies – Factor VIII product differences
- **Domperidone** and cardiac risk
- **Sodium valproate** and developmental disorders following use in pregnancy
Codeine for analgesia in children

The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA has recommended that use of codeine-containing medicines in children be restricted to those aged over 12 years with acute moderate pain that cannot be relieved by other analgesics, for example, paracetamol or ibuprofen.

In addition, codeine should never be used for children under 18 years undergoing tonsillectomy or adenoidectomy to treat obstructive sleep apnoea. The prescribing information will also be updated to contraindicate codeine in conditions associated with impaired breathing.
Numeta 13% and hypermagnesaemia

Numeta 13% parenteral nutrition for preterm babies

Signal of 14 reports from MAH of hypermagnesaemia – July 2013

Voluntary recall of Numeta 13%

PRAC concluded advice in September 2013 to suspend Numeta 13%, introduce risk management for Numeta 16%
Kogenate and Helixate & inhibitor development

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Factor VIII Products and Inhibitor Development in Severe Hemophilia A

Samantha C. Gouw, M.D., Ph.D., Johanna G. van der Beek, M.D., Rolf Ljung, M.D., Ph.D., Carmen Escuriola, M.D., Anna Ségolène Claeyssens-Donadel, M.D., Christel van Geffen, M.D., Gili Kenet, M.D., Anne Mäkipernaa, M.D., Ph.D., Angelo C. Fregni, M.D., Wolfgang Muntean, M.D., Rainer Kobelt, M.D., Georg Elena Santagostino, M.D., Ph.D., Angela Thomas, M.D., and H. Marijke van den Berg, M.D., Ph.D. for the PedNet and RODIN Study Group

ABSTRACT

BACKGROUND
For previously untreated children with severe hemophilia A, the type of factor VIII product administered and switching associated with the development of clinically relevant inhibitor development.

Figure 2. Adjusted Relative Risk of Inhibitor Development, According to the Type of Factor VIII Product.
Domperidone and CVS risk

- Cardiac safety reviewed by PRAC after data accrued
- Large pharmepi study confirmed increased risk of sudden cardiac death in over 60s
- Restriction of indication to nausea and vomiting, dose restriction and duration limit
- Data on efficacy in children to be generated
Sodium valproate in pregnancy & persistent developmental delay

- Indications include epilepsy, bipolar disorder & migraine
- Use in women of child bearing potential varies across Europe
- Nature and magnitude of risk needs to be better understood
- Effectiveness of risk minimisation
Conclusions from PRAC referrals in paediatric population

- Need for specialist paediatric input to interpret data on benefits and harms, need for perspective of children and parents/carers
- Need for early planning for stakeholder involvement when referral notified
- Where robust data are lacking, may need to require studies to be done
- Special challenge of interpreting potential harms in child from pregnancy exposure
Newly started PRAC referrals

- **Codeine for cough/cold** and risk of toxicity in CYP 2D6 ultra-rapid metabolisers

- **Ambroxol/bromhexine** and risk of serious skin reactions

- **Testosterone** and cardiovascular risk

- **Hydroxyzine** and cardiovascular risk
## Signals in paediatric population

<table>
<thead>
<tr>
<th><strong>Safety Issue</strong></th>
<th><strong>Data source</strong></th>
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<tbody>
<tr>
<td>Paracetamol – pregnancy use</td>
<td>• Published study</td>
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<tr>
<td>Cinacalcet - hypocalcemia</td>
<td>• Clinical study</td>
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<tr>
<td>Dexmedetomidine – apnoea</td>
<td>• EudraVigilance</td>
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<tr>
<td>Somatropin – convulsions</td>
<td>• EudraVigilance</td>
</tr>
<tr>
<td>Sertraline – growth retardation</td>
<td>• Published study</td>
</tr>
<tr>
<td>Fentanyl patches: accidental exposure</td>
<td>• FDA communication</td>
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</tbody>
</table>
Fentanyl Patch Can Be Deadly to Children

Mother enters plea in connection with death of son
WMUR Manchester - 2 days ago
...that Davis failed to properly secure a fentanyl patch that was accidentally transferred from her body to her 7-month-old child in July 2011.
Vaccine signals in paediatric population

- **Pandemrix** and risk of narcolepsy
- **HPV vaccine** [types 16, 18] - signal of complex regional pain syndrome
- **HPV vaccine** [type 16, 18] - signal of primary premature ovarian failure
- **HPV vaccine** [type 6, 11, 16, 18] – signal postural orthostatic tachycardia
- **HPV vaccine** [types 6, 11, 16, 18] - Bronchospasm in patients with or without asthma

- PASS
- Spontaneous ADRs
- Spontaneous ADRs
- Spontaneous ADRs
Incoming PRAC signal in paediatric population

Aqueous 2% chlorhexidine-induced chemical burns in an extremely premature infant

Arch Dis Child Fetal Neonatal Ed: F64 January 2012
Conclusions from PRAC signals in paediatric population

- Different ADR patterns
  - Need for case definitions
  - Need for accurate age in ICSRs
- Importance of literature monitoring as specialists tend to publish rather than report ADRs
- Long term effects including developmental disorders
- Pregnancy exposure
- Importance of published literature as resource
- Adapted approaches for vaccines to support rapid signal validation
Risk management plans in paediatric population

- Example – Haemangiol (propranololol 3.75 mg/ml) for treatment of proliferating infantile haemangioma
- PRAC advised on RMP and considered recruitment into PASS study
Post authorisation safety studies in paediatric population

Example – Ivacaftor

PRAC advised on a long-term observational study

To include microbiological and clinical endpoints (e.g. exacerbations)

PRAC’s conclusions from proactive pharmacovigilance in paed population

• PRAC needs better knowledge of PDCO recommendations of risk management systems
• PIPs and RMPs need to be integrated as a continuum
• Facilitate involvement of ENCePP paediatric network
• Better awareness of work of Enpr-EMA network
Challenges in paediatric pharmacovigilance

- Likely extensive underreporting of suspected adverse reaction reports in children
- Concern that risk of ADRs greater in off-label use in children
- Medication errors more frequent and more serious in paediatric population
- As new medicines become available for paediatric population, must *shift from reactive to proactive*, demonstrate effectiveness of risk minimisation
- Adapting pharmacovigilance communications to paediatric population’s needs
Survey of ADR reporting rates 2002
Evidence on ADRs in off-label and unlicensed use in children

Off-label and unlicensed medicine use and adverse drug reactions in children: a narrative review of the literature

Jennifer Mason, Munir Pirmohamed, Tony Nunn

DOI 10.1007/s00228-011-1997-1

Abstract The use of unlicensed and off-label medicines in children is common because trials in children have not usually been performed during the drug development process. Consequently, the information available to paediatricians may not always be as detailed or as robust as that available when prescribing a medicine that is licensed for that has received some attention in this population is the use of off-label and unlicensed medicines [3]. The necessity of using off-label and unlicensed medicines in children is a consequence of how, historically, medicines have been developed and regulated.
PRAC approach to addressing challenges of pharmacovigilance in paediatric population

- Using “tools” of Pharmacovigilance legislation to fullest potential for paediatric population
- Operating an effective interface between paediatric and pharmacovigilance systems, PDCO and PRAC
- Better science - building relationships and interactions with academia and research networks
- Optimising the contribution and value-added of public and patients
PhVig legislative tools relevant to the paediatric population

- Expanded definition of ADR including off-label, unlicensed, error and misuse
- Member states to encourage ADR reporting
- Additional monitoring system
- Signal detection systems
- Urgent decision-making referrals
- Risk management plans for all new MAs
- PASS and PAES studies
- Transparency and communication
- Stakeholder involvement
How well are PhVig legislative tools being used for paediatric population?

- Ad hoc consideration by PRAC of benefit risk in paediatric population rather than systematically
- Usually later in referral procedures or after completion – getting earlier
- Guideline on pharmacovigilance in paediatric population requires updating to reflect new legislation
Current opportunities to strengthen pharmacovigilance in paediatric population

• Getting messages across about importance of ADR reporting – additional monitoring and patient reporting

• Adapting signal detection to paediatric population, especially in area of vaccines

• Incorporating patient and public views in referrals

• Focus on better science – supporting research in paediatric population - involving ENCePP paediatric network and Enpr-EMA
Did you know?
You can report side effects yourself

As a patient, you have the right to report unwanted side effects of medicines directly to the authorities. You can also report a side effect on behalf of someone in your care, such as a child or relative.

Remember to speak to your doctor or pharmacist if you are worried about any suspected side effects.

Why report a side effect?
We are always learning more about medicines. Although they are tested extensively in clinical trials before they are authorised, not everything can be known about their side effects.

How do I report a side effect?
If you think a medicine has caused a side effect, please check the package leaflet that comes with the medicine for information on how to report it.
Patients’ contribution to ADR reporting

* Pre legislation data period - 02/07/2011 - 01/07/2012
** Post legislation data period - 02/07/2012 - 01/07/2013
New signal detection methodologies in vaccine vigilance

Maximised sequential probability ratio testing for observed vs expected signals

Donegan et al 2013, Vaccine 31, 43, 4961-7
Maximised SPRT for ME/Chronic Fatigue Syndrome for girls aged 12/13 years (2008-2009)

Week of Surveillance

Log Likelihood Ratio

Critical value
- 10% events reported
- 25% events reported
- 50% events reported
- 75% events reported
- 100% events reported

Week of Surveillance
Long term safety - EU Funding

ADDUCE
Attention Deficit Hyperactivity Drugs Use Chronic Effects

Home The ADDUCE Consortium The ADDUCE Project What is ADHD?

Home

ADDUCE studying long-term safety in ADHD treatment

The Adduce studies (Attention deficit/hyperactivity disorder drugs use chronic effects) address the EU 7th framework Health work program “Adapting off-patent medicines to the specific needs of paediatric population”. Methylphenidate is a widely prescribes stimulant in ADHD. The ADDUCE studies address will provide information on the long term side-effects in children and adolescents and cardiovascular effects in adults.

Click to read more

Long term effects methylphenidate in ADHD

Medicines use in pregnancy

Long term adverse effects of immunomodulators

Suicidal behaviour and various drugs/classes
Medicines information for children and young people — a forward step

In this article, Nicola Gray and colleagues describe the development of a patient information leaflet that contains specific information for children.

This info is to help you learn the main things about your medicine called [product]. If you don’t enjoy reading, someone like your mum, dad or carer (sometimes called “your guardian”) can read it to you and answer any questions.

It may help if you read small bits at a time.
Effectiveness of risk minimisation example - desmopressin

Impact of action to remove indication of nocturnal enuresis for desmopressin nasal spray
Summary of PRAC perspective

- Some progress in addressing the special challenges for pharmacovigilance in paediatric populations

- Mismatch between CT population and real life use in paediatrics means a significant knowledge gap

- Pharmacovigilance legislative tools create significant potential to minimise harms in paediatric population from strengthened systems

- Paediatric population issues need to be considered in all phases of the pharmacovigilance cycle
Priorities for Paediatric Pharmacovigilance

- Promote reporting ADRs in children - networks of paediatric centres?
- Pilot new approaches to strengthen signal detection
- Press ahead with work on medication error
- Promote research networks – including pregnancy
- PRAC/PDCO collaborative working on benefit risk throughout product lifecycle