Pharmacovigilance Paediatric Perspective

To give insight into the specifics of reviewing pharmacovigilance reports for children

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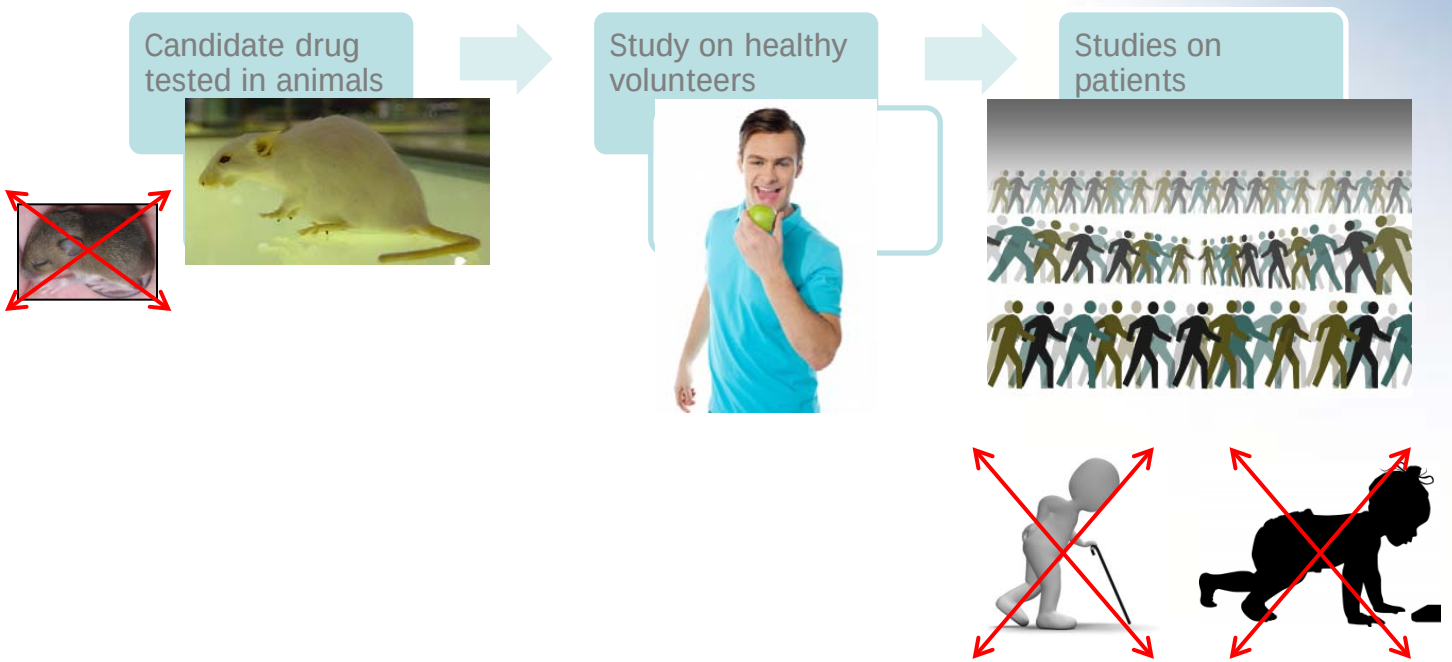
the UPPSALA MONITORING CENTRE

Patient harm

- Medicines can cause patient harm resulting from
  - pharmacological effect (adverse effect)
  - individual patient idiosyncrasy (adverse reaction)
  - suboptimal medication use and practice

Pre-marketing activities (most often)



homogeneity

Image courtesy of [stockimages, africa, Stuart Miles, sattva]/FreeDigitalPhotos.net and http://animalphotos.info/a/topics/animals/mammals/rodents/mice/

Lack of product information

If children are excluded in clinical studies

Limited product information specific for children

- dosing
- warnings
- precautions
- adverse drug reactions (ADR)

 extra consideration!

Constant change during childhood

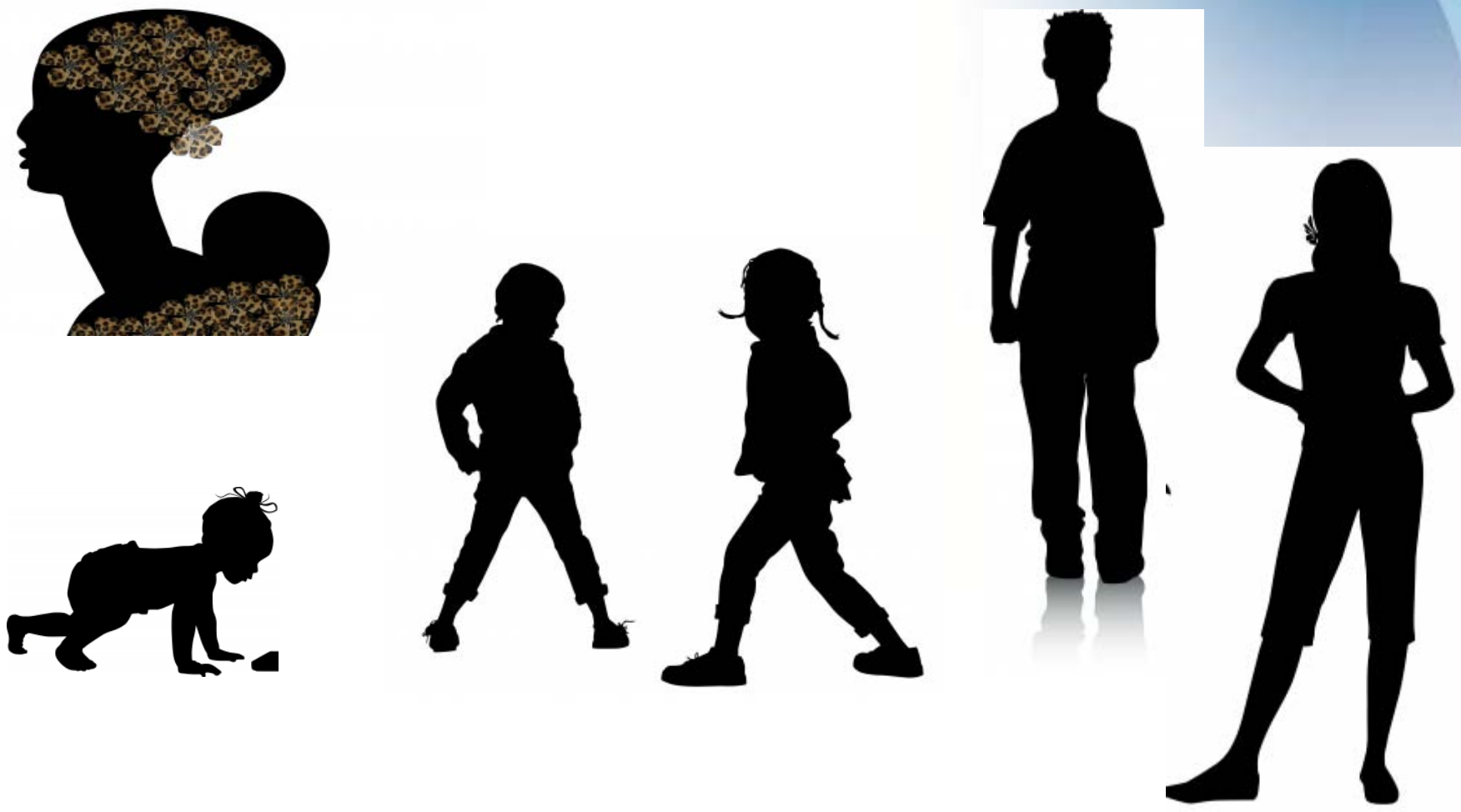


Image courtesy of africa, sattva / FreeDigitalPhotos.net

Children are not small adults

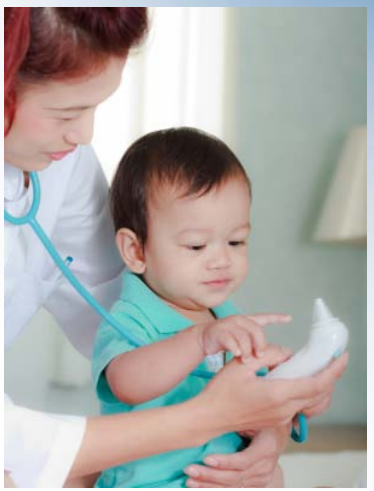
- Differ **biologically**
  - Medicine absorption, distribution, metabolism and excretion[1]
  - Hormone activity[2]
- Differ **psychosocially**
  - Dependence to independence
  - Limited communicational skills to full ability

Impact dosing, administering and monitoring

1) Kearns GL et al. N Engl J Med. 2003; 349(12):1157-67.
2) Kennedy M. Clin Pharmacol Ther. 2008 84(6):662-73.

Medication in paediatrics

- Calculation for each individual child
- Dilution
- Small amounts
- Extemporaneous preparations



- Different risk benefit profile
- Long term effects

Image courtesy of Sura Nualpradid/ FreeDigitalPhotos.net

Situation in Paediatrics

- Off-label use (use not supported by product description)[1]
  - 18 – 65% in hospital care
  - 11 – 31% in out-patient care
- Lack of age-suitable dosage forms
  - 22-25% of medications indicated for children lacked appropriate dosage forms[2]

1) Kimland E, Odlind V. Clin Pharmacol Ther. 2012; 91(5):796-801. (Review of studies)
2) Tan E et al. Med J Aust. 2003; 179(4):195-8. (Australian study)

Example: Captopril 12.5 mg tablets

Initial starting dose
Children: 0.3 mg/kg
Premature, newborn and infants: 0.15 mg/kg

Summary of Product Characteristics

SPC Captopril 12.5 mg Tablets

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2. Qualitative and quantitative composition | Go to top of the page

Each tablet contains captopril, 12.5mg.

For a full list of excipients, see section 6.1

3. Pharmaceutical form | Go to top of the page

Tablet

White to off-white, round, flat, beveled edged, uncoated tablet with inscription ' BG ' on one side and plain on other side.

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4.2 Posology and method of administration | Go to top of the page

For Oral Administration

Dose should be individualised according to patient's profile (see section 4.4) and blood pressure response. The recommended maximum daily dose is 150 mg.

Captopril may be taken before, during and after meals.

Adults

Hypertension: Treatment with captopril should be at the lowest effective dose which should be titrated according to the needs of the patient.

The recommended starting dose is 25-50 mg daily in two divided doses. The dose may be increased incrementally, with

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Elderly

As with other antihypertensive agents, consideration should be given to initiating therapy with a lower starting dose (6.25 mg BID) in elderly patients who may have reduced renal function and other organ dysfunctions (see above 'renal impairment' and section 4.4.)

Dosage should be titrated against blood pressure response and kept as low as possible to achieve adequate control.

Children and adolescents

The efficacy and safety of captopril have not been fully established. The use of captopril in children and adolescents should be initiated under close medical supervision.

The initial starting dose should be 0.3 mg per kg body weight. .For patients requiring special precautions (children with renal dysfunction, premature infants, new-borns and infants, because their renal function is not the same with older children and adults) the starting dose should be only 0.15 mg captopril/kg weight. Generally, captopril is administered to children 3 times a day, but dose and interval of dose should be adapted individually according to patient's response.

4.3 Contraindications | Go to top of the page

Situation in Paediatrics

- Potentially harmful medication errors occur more within paediatrics than in adult care[1]
- Incidence of ADRs in children[2]
  - 10.9% (4.8-17.0) of inpatients
  - 1.0% (0.3-1.7) in primary care
  - 1.8% (0.4-3.2) of hospital admissions

1) Kaushal R et al. JAMA. 2001; 285(16):2114-20. US prospective study
2) Clavenna A, Bonati M. Arch Dis Child. 2009; 94(9):724-8. Review of 8 prospective studies (primarily EU)

Background calls for action

- Medicines need to be developed and studied specifically in children
- Monitoring for ADRs important
- Pharmacovigilance reports valuable

Results from a review on reports for children worldwide

ORIGINAL RESEARCH ARTICLE

Drug Saf 2011; 34 (5): 415-428
0114-5916/11/0005-0415/$49.95/0

Suspected Adverse Drug Reactions Reported For Children Worldwide

An Exploratory Study Using VigiBase

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Abstract

Background: As a first step towards implementing routine screening of safety issues specifically related to children at the Uppsala Monitoring Centre, this study was performed to explore reporting patterns of adverse reactions in children.

Objective: The first aim of this study was to characterize and contrast child

Objective

Explore VigiBase data to prepare for routine screening of reports for children

1. To characterise reports for children
2. Type of adverse reactions recently reported with a greater frequency by age group (2005 -Feb 2010 compared with 1995-1999)

Overall ADR review

A low proportion of reports for children (0-17 years)

- 7.7% of VigiBase reports, vaccine reports excluded

A higher proportion of reports for children in

- Latin America (15%), Africa (15%), Asia (14%)

than in

- North America (7%), Oceania (7%), Europe (7%)

Most reported reactions and medicines in children

- Skin reactions (35%)
- Anti-infective medicines (33%)

Pattern of reported reactions by age group

reported more frequently during recent years

0 to 27 days 	28 days to 23 months 	2 to 11 years 	12 to 17 years 
Premature baby	Erythema	Drug ineffective	Drug ineffective
Neutropenia	Pruritus	Erythema	**Suicidal ideation**
Neonatal disorder	Irritability	Decreased appetite	**Suicide attempt**
Anaemia	**Medication error**	Psychomotor hyperactivity	**Completed suicide**
Blood lactic acid increased	Drug ineffective	Abdominal pain upper	Depression
Foetal growth retardation	**Accidental overdose**	Aggression	Erythema
Medication error	**Drug toxicity**	Somnolence	Nausea
Hypertriglyceridaemia	Lethargy	Crying	Intentional overdose
Feeding disorder neonatal	Eyelid oedema	Suicidal ideation	Loss of consciousness
Anaemia macrocytic	Respiratory arrest	**Medication error**	Feeling abnormal

Age groups defined according to European Medicines Agency. ICH Topic E 11. Clinical Investigation of Medicinal Products in the Paediatric Population. January 2001 CPMP/ICH/2711/99.

Conclusion
Reports for children worldwide

Planned screening of VigiBase reports for children will give particular focus to:

- serious skin reactions
- events related to medication errors
- psychotropic medicines
- geographical regions with higher reporting for children

Reflections on reports for children

- Reports concerning **congenital birth defects** often lacked age or was recorded with mother age
  - E2B parent-child/foetus reports preferred
- **Prematurity** not determined by age field
  - weight field and narrative important
- **Strength**, **route** of administration and **dosage form**
  - important to report for children

Reflections on reports for children

- High proportion of vaccine reports – 46% for ages 0-17 years (data up to Feb 2010)
- Quantatively challenging to differentiate reports concerning problems in newborns resulting from
  - drug exposure in utero
  - via breast milk
  - newborns' own drug intake

Planning for signal detection in VigiBase data for children

- Retrospective review of signals: 4% concerned children
- The aim of signal detection in VigiBase data for children will be to
  - Take advantage of the uniqueness of VigiBase (reports on children in each nation might be few)
  - Avoid doing duplicate work along with the national centres
- Current routine signal detection focuses on
  - New drugs (old drugs commonly used for children)
  - Not labelled reactions (might not be known for children)

Planning for signal detection in VigiBase data for children

- Contributing with further knowledge for rare and serious reactions (known or unknown)
- Detecting the unexpected and unrecognised by child age group

Safety, medicines and medication in paediatrics

- A medicine can be considered safe but is it safe for children?
- Considerations on medication use and practice in paediatrics is important!