What is Paediatric Clinical Pharmacology?

Professor Imti Choonara
The scientific study of medicines in children
• Formal training programme
• Accreditation of Derby as training centre
• First accredited trainee-2006
Training (UK)

- Medical graduates
- Subspecialty of paediatrics
- Approved in 2003
- 3 year training programme
Training programme

- Regulatory aspects
- Socio-political
- Rational use of medicines
Curriculum

- Clinical trials
- Ethics
- Pharmacokinetics
- Drug metabolism
- Drug toxicity
- Rational use of medicines
Drug toxicity

- Chloramphenicol  1959  Grey baby syndrome
- Thalidomide  1961  Phocomelia in newborn
UK

- Medicines Act, 1968
- Licensing of medicines
Off-label

Used in a different manner to licensed recommendations
Off-label

• Indication
• Dose
• Age
• Route
Unlicensed and off label drug use in paediatric wards: a prospective study

Turner et al, BMJ 1998
- 707 admissions
- 256 patients (36%) received unlicensed or off label treatment in hospital

*Turner, 1998*
Safeguards ‘ignored’ on drugs for children
Unlicensed and off label drug use in neonates

Conroy et al, Arch Dis Child 1999
• 70 babies

• 63 (90%) received an unlicensed or off label medicine

Conroy, 1999
Doctors raise alarm over drugs given to babies

Sarah Boseley
Health Correspondent

Babies are at their most vulnerable in the days after birth, yet the sickest, in hospital intensive care units, are more likely than older children to be given medicines that have not been tested for their effects on a child’s body, according to research published yesterday.

The doctors and medical academics from Nottingham University and Derbyshire Children’s Hospital warned that something must be done before a tragedy occurs. “Urgent action is required to resolve this situation,” they said.

Because of fears of harming children in clinical trials and because of the extra cost, drug companies do not generally investigate the likely impact of their medicines on a child, let alone a week-old baby. They prefer not to apply for a licence for a drug’s use in children, leaving doctors to decide what to give a child and estimate the right dose.

The study of 70 babies admitted to neonatal intensive care in 1998, published in the Archives of Disease in Childhood, reveals that 90 per cent were given drugs that were either unlicensed for children or prescribed ‘off-label’ — in doses or for diseases for which they are not approved.

Sharon Conroy, of the academic division of child health at Nottingham University and colleagues, the authors of the research, point out that the information in a drug licence stipulates how it can be safely used. Yet nine out of ten of the most prescribed medicines on the babies’ ward were in unlicensed use. “This highlights the inadequacies of the current licensing framework,” they write.

The most common drugs given to these tiny sick babies were gentamicin and Benzyl penicillin, which are used in septicaemia and meningitis. The authors note that gentamicin is highly toxic and under-developed kidneys cannot get rid of it in the same way that adult organs can. The doses of both drugs used on children can vary greatly from one hospital to another.

In 1997, the Commons health committee said it was wrong that doctors had to guess the dose of an adult drug to give a child. The MPs called for clinical trials to test drugs for safety in children.
Survey of unlicensed and off-label drug use in paediatric wards in European countries

Conroy et al, BMJ 2000
<table>
<thead>
<tr>
<th>Location</th>
<th>Patients</th>
<th>% Receiving UL/OL Medicines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Derby</td>
<td>192</td>
<td>57</td>
</tr>
<tr>
<td>Uppsala</td>
<td>87</td>
<td>43</td>
</tr>
<tr>
<td>Marburg</td>
<td>85</td>
<td>54</td>
</tr>
<tr>
<td>Bergamo</td>
<td>118</td>
<td>86</td>
</tr>
<tr>
<td>Rotterdam</td>
<td>142</td>
<td>90</td>
</tr>
<tr>
<td>TOTAL</td>
<td>624</td>
<td>67</td>
</tr>
</tbody>
</table>
Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study

Turner et al, Acta Paediatr 1999
‘We are concerned that as evidence-based medicine is becoming widely accepted children continue to be ignored.’

Bonati et al

Lancet, 1999
‘We believe that children have the same rights as adults to receive medicines that have been formally tested to ensure efficacy and safety’.

Bonati et al

Lancet, 1999
'To improve such a situation, the joint effort of governmental organisations, the pharmaceutical industry, and any relevant bodies or individuals is mandatory'.

Bonati et al
Lancet, 1999
Outcome

• European Regulation 1901/2006 on Medicinal Products for Paediatric Use
• Came into effect on 26 January 2007
European Legislation

- Children’s rights
- Pharmaceutical industry profits - $35 million per drug (with paed exclusivity)
US legislation

• 1997 FDA Modernization Act
• 1998 Pediatric Rule
• 2002 Best Pharmaceuticals for Children Act
• 2003 Pediatric Research Equity Act
FDAMA’s written request list: medicines for children

Jong et al, Lancet 2001
<table>
<thead>
<tr>
<th>Drug Category</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>26</td>
</tr>
<tr>
<td>Antiviral</td>
<td>9</td>
</tr>
<tr>
<td>Analgesics</td>
<td>9</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>6</td>
</tr>
<tr>
<td>Asthma</td>
<td>5</td>
</tr>
<tr>
<td>Lipid Regulation</td>
<td>4</td>
</tr>
<tr>
<td>GIT</td>
<td>4</td>
</tr>
</tbody>
</table>
Stimulation programs for pediatric drug research – do children really benefit?

Boots et al,
Eur J Pediatr 2007
Medicines granted exclusivity reflected adult use (not paediatric)

Boots, 2007
<table>
<thead>
<tr>
<th>Country</th>
<th>2000</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>9</td>
<td>8</td>
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<tr>
<td>Canada</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Cuba</td>
<td>9</td>
<td>6</td>
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</tbody>
</table>

WHO, 2012
European Regulation

- Medicines used to treat paediatric patients are subject to ethical research of high quality
- These medicines are authorised
European Regulation

- Without subjecting the paediatric population to unnecessary clinical trials
- Without delaying authorisation of medicines for adults
Paediatric Committee

Will they be able to stop clinical trials of ‘me-too’ drugs in children?
Pharmacokinetic studies
How many blood samples do you need?
Stereoselective interaction between the R enantiomer of warfarin and cimetidine

Choonara et al, Br J Clin Pharmacol 1986
Drug interaction study

- 8 volunteers
- 4 part study
- R, R + C, S, S + C
- Oral dose of warfarin
- Cimetidine (±)
- Vitamin K IV

Choonara, 1986
Drug interaction study

• Blood samples 18 x 4
• Warfarin
• Vitamin K
• Vitamin K 2,3-epoxide
• Prothrombin time

Choonara, 1986
Midazolam PK

- 25 studies
- Neonates - adolescents
- Blood samples 1-14
- Median 8
Population PK

- Larger number of pt
- Smaller number of samples
Ethics of clinical trials in children
Propofol

Sedation in PICU

- 1992 Case reports of metabolic acidosis
- 1992 CSM advised against use
- 1998 Review of 15 deaths
Propofol

- Sedation in critically ill children
- American RCT
- 21 deaths (9%) – propofol
- 4 deaths (4%) – standard sedation

Roberts et al, JAMA 2003
American Propofol Study

- No ISMB/DMC
- Dose too high (5.5 mg/kg/h)
- No recognition of toxicity
A systematic review of safety monitoring and drug toxicity in published randomised controlled trials of antiepileptic drugs in children over a 10-year period

Anderson et al, Arch Dis Child 2010
• 29 trials adults and children
• Only 10 stated number of children recruited
• Only 3 analysed paediatric patients separately

Anderson, 2010
“…..data for children recruited into clinical trials alongside adults should always be reported separately in relation to efficacy and safety”.

Anderson et al, Arch Dis Child 2010
Drug toxicity in children

- Sulphonamide 1956
- Chloramphenicol 1959
- Sodium valproate 1979
- Salicylate 1980
- Propofol 1992
- Ceftriaxone 2006
A difference in mortality rate and incidence of kernicterus among premature infants allotted to two prophylactic antibacterial regimens

Silverman et al, Pediatrics 1956
<table>
<thead>
<tr>
<th></th>
<th>Treated</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxytetracycline</td>
<td>97</td>
<td>34</td>
</tr>
<tr>
<td>Penicillin &amp;</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td></td>
<td>74</td>
</tr>
</tbody>
</table>

*Silverman, 1956*
Sulphonamides

• Highly protein bound
• Displace bilirubin from albumin
• Increase free bilirubin
• Increase risk of kernicterus

Dunn, 1964
• Avoid highly protein bound drugs
Fatal cardiovascular collapse of infants receiving large amounts of chloramphenicol

Sutherland,
Am J Dis Child 1959
Chloramphenicol in the newborn infant. A physiologic explanation of its toxicity when given in excessive doses

Weiss et al, NEJM 1960
Chloramphenicol

- Impaired metabolism in neonate
- Dosage reduction from 100 to 50 mg/kg daily

Weiss, 1960
• Is drug metabolism impaired in the patient population?
Sodium valproate

- Hepatotoxicity
- Reported in 1979
- >100 deaths
- Mainly in children
Valproic acid hepatic fatalities: a retrospective review

Dreifuss et al, Neurology 1987
Valproic acid

- 37 deaths

Risk factors
- Age < 3 years
- Polypharmacy
- Developmental delay

Dreifuss, 1987
Do **not** use valproic acid as first line anti-epileptic drug in children at greatest risk •Age <3 years •Polypharmacy •Developmental delay
Reye’s syndrome

• 31 cases reported
• 15 treated with aspirin

Giles, Lancet 1965
Reye’s syndrome and salicylate use

Starko et al, Pediatrics 1980
Reye’s syndrome

- Influenza A outbreak
- 7 schoolchildren admitted
- 16 controls (same class)

Starko, 1980
Reye’s syndrome

• More salicylate containing medicines
• Larger doses
• Salicylates more frequently
• Correlation between severity of illness and salicylate consumption

Starko, 1980
Reye’s syndrome

• Avoid salicylates for common febrile illnesses in children
Propofol

- 5 deaths
- Case reports
- Croup (4)
- Bronchiolitis

Parke et al, BMJ 1992
Propofol infusion syndrome in children

- 15 deaths
- Long term > 48h
- High dose > 4 mg/kg/h

Bray, *Paed Anaesth* 1998
**Propofol**

- Do **not** use as a sedative in critically ill children
Anaphylactoid shock or precipitation of calcium-ceftriaxone in a premature newborn. A case report

Belliard et al, Arch Pédiatrie 2006
Intravenous ceftriaxone and calcium in the neonate: assessing the risk for cardiopulmonary adverse events

Bradley et al, Pediatrics 2009
Ceftriaxone

• 9 cases in USA
• 7 ≤ 2 months old
• 7 deaths
Ceftriaxone

- Highly protein bound
- Why use in neonates?
How frequent are ADRs?
Incidence of adverse drug reactions in paediatric in/out patients: a systematic review and meta-analysis of prospective studies

• Overall incidence of ADRs 9.5% in children in hospital
• 12.3% of ADRs severe
• 2.1% paediatric hospital admissions due to ADRs

Impicciatore, 2001
How frequent are ADRs in the community?
Adverse drug reactions in children in Camagüey Province, Cuba

Z Bárzaga Arencibia, D Novoa Sotomayor, N Caballero Mollinedo, I Choonara, E Fernández Manzano, A López Leyva


ABSTRACT

Objective To determine the incidence of adverse drug reactions (ADRs) in children in Camagüey Province, Cuba.

Methods A national pharmacovigilance programme has been established in Cuba and involves suspected ADRs being reported to provinces. All suspected ADRs reported to Camagüey Province during 2008 were analysed and classified in relation to causality and severity.

Results Over a 12-month period, there were 124 reports of 152 suspected ADRs in children. Most ADRs were mild (98, 79%), but two were fatal and five others were severe. Antibiotics were the group of medicines most likely to be associated with ADRs. The overall report rate of suspected ADRs was 634 per million children per year, which is considerably higher than previously reported rates.

Conclusions ADRs in children are more frequent than previously reported. A successful pharmacovigilance programme can be established in lower middle income countries.

What is already known on this topic

- Adverse drug reactions (ADRs) occur in 1 in 10 children in hospital.
- ADRs in children, both in hospital and in the community, are under-reported.

What this study adds

- The incidence of ADRs in children in Cuba (634 reports per million children per year) is far greater than previously reported.
- Successful pharmacovigilance programmes can be established in lower middle income countries.
### ADRs reported in children in Camagüey Province (2008)

<table>
<thead>
<tr>
<th>ADR</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drowsiness</td>
<td>21</td>
<td>14</td>
</tr>
<tr>
<td>Headache</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Respiratory distress/failure</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Tremor</td>
<td>15</td>
<td>10</td>
</tr>
</tbody>
</table>
ADR rates/million children/years

Denmark 222
Spain 165
Sweden 226
UK 182
Cuba 634
• Few reports from secondary care
• No reports for anticonvulsants or cytotoxic agents
Education

• Targeted at health professionals in community and hospital
• Education on drug toxicity
• Importance of reporting ADRs
• Involvement of a hospital Drug & Therapeutics Committee
ADR reports

Year | Count
--- | ---
2008 | 100
2009 | 150
2010 | 350
Hospital reports

Year | 2008 | 2009 | 2010
---|---|---|---
Value | 10 | 15 | 130
Pharmacovigilance in children in Camagüey Province, Cuba

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e-mail: imti.choonara@nottingham.ac.uk
Pharmacovigilance

- Number of ADR reports increased after education
- 2031 reports per million children per year
- Highest reporting rate for children in the world
ADR rates/million children/years

Denmark 222
Spain 165
Sweden 226
UK 182
Cuba 2031
Rational use of medicines is important
Propofol

Sedation in PICU

• 1992 Case reports of metabolic acidosis
• 1992 CSM advised against use
• 1998 Review of 15 deaths
• 1999 Fatality in UK
Sodium valproate

• 1978 Case reports of hepatotoxicity
• 1987 Guidelines – age, polypharmacy, developmental delay

4 fatalities in UK in children aged 2 years or under

Clarkson, 2002
Cuba, Camaguey Province 2009-10

- ADRs to analgesics - 50
- Dipyrrone - 32
- NSAIDs - 12
- Paracetamol - 6
Which medicines do children need?
Diabetes mellitus

• Type 2 increasing in adolescents

• How many oral hypoglycaemic agents should we study?
WHO

• Two million children die each year from pneumonia
• One million children die each year due to malaria

Why?
WHO

Access ensuring children receive medicines:

- Analgesia
- Oral rehydration therapy
- Antibiotics for pneumonia
- Asthma medication
Malaria

- 800,000 children < 5y die each year
- 90% cases in Africa
- Need for new medicines?
- Lack of access to medicines and health care
Children’s access to treatment for epilepsy: experience from the Lao People’s Democratic Republic

Bareenss et al, Arch Dis Child, 2011
90% of children with epilepsy in Lao do not receive treatment

Barenesses et al, 2011
Why children with epilepsy may not receive treatment

- Parent’s stigma
- Parent’s poor understanding of epilepsy
- Difficulty accessing health care
Children need medicines that are evidence based AND need access to medicines and health care