Consideration on the dose selection in different age groups and on safety

AGAH Workshop, Bonn, 13.-14.01.2009:

PAEDIATRIC INVESTIGATION PLAN -
How to Adapt Clinical Development to the Particularities of Paediatrics?
Agenda

Required Decisions for PIPs on Authorised Products

- Paediatric developmental pharmacology aspects
- Lessons learned from existing experience
  - Paediatric clinical experts (Europe, US)
  - Off-label use of a variety of drugs
- Safety considerations – specific paediatric safety possible or necessary for PIP
Off label use – Deficits of clinical studies

- Lack of paediatric dose recommendation in the SPC
  (Need: Finding the appropriate dose)  Phase 1
- Lack of efficacy data in different age groups
- Lack of drug formulations adequate for paediatric patients
  (Need: age-appropriate formulations)
- Lack of information on specific paediatric adverse drug reactions  Phase 3/4
- Delayed access to new therapies (e.g. AIDS, antirheumatics)
Age groups according to ICH 11 and EMEA

- Neonates
  - Pre-term newborns
  - Term newborns/neonates
- Infants + Toddlers
- Children -
  - Preschool children
  - School children
- Adolescents

0 to 27 days
< 36th weeks of gestation
0-27 days
28 days to 23 month
2 to 11 years prior to puberty
2 to 5 years
6 to 11 years
12 to 17 years
Dose finding considerations

- Is extrapolation from adult data possible?
  Similar pharmacodynamics as in adults
  Valid clinical study endpoints
    - Blood pressure
    - Heart rate
    - Respiration – oxygen saturation
  Biomakers (valid and tested for predictability)

- Is extrapolation from adult data impossible?
  Different pharmacodynamics
  Different diseases
Calculation of the dose according to the dosing in adults

ECFV = distribution  \[ ND_{\text{child}} = ND_{\text{adult}} \times \frac{\text{BSA}_{\text{child}}}{1.73 \text{ m}^2} \]

<table>
<thead>
<tr>
<th>Years</th>
<th>Calculation adult dose</th>
<th>Dose/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>1/5</td>
<td>1.8</td>
</tr>
<tr>
<td>1</td>
<td>1/4</td>
<td>1.6</td>
</tr>
<tr>
<td>3</td>
<td>1/3</td>
<td>1.5</td>
</tr>
<tr>
<td>7.5</td>
<td>1/2</td>
<td>1.4</td>
</tr>
<tr>
<td>12</td>
<td>2/3</td>
<td>1.2</td>
</tr>
<tr>
<td>Adult</td>
<td>1</td>
<td>1.0</td>
</tr>
</tbody>
</table>
**Pharmacokinetics** → **Pharmakodynamics**

- Absorption
- Distribution
- Metabolism
- Excretion

**Plasma**

**Effect**

**Time for significant physiological adaptation:**

<table>
<thead>
<tr>
<th>Process</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>1 – 12 month</td>
</tr>
<tr>
<td>Distribution</td>
<td>1 – 6 (12) years</td>
</tr>
<tr>
<td>Metabolism</td>
<td>3 month</td>
</tr>
<tr>
<td>Excretion</td>
<td>3 month</td>
</tr>
</tbody>
</table>

**Measures:**
- $V$ (l/kg)
- $t_{1/2}$ (min)
- $Cl$ (ml/min)
- AUC
Changes in body composition

Distribution of the drugs in various compartments

Extracellular Water

Intracellular Water

Protein

Fat

Preterm neonate

4 mo.

12 mo.

24 mo.

36 mo.

Adult

Percent of body weight

Kaufman, Pediatric Pharmacology (Yaffe & Aranda, eds) pp. 212-9, 1992
Metabolic capacity related to age and body weight
**Pharmacokinetics:**
Elimination half-time ($t_{1/2}$) according to age

<table>
<thead>
<tr>
<th>Drug</th>
<th>Newborn</th>
<th>Infant</th>
<th>Child</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>4.0</td>
<td>1.7</td>
<td></td>
<td>1.0 – 1.5 h</td>
</tr>
<tr>
<td>Piperacillin</td>
<td>0.8</td>
<td>0.5</td>
<td>0.4</td>
<td>0.9 h</td>
</tr>
<tr>
<td>Diazepam</td>
<td>30</td>
<td>10</td>
<td>25</td>
<td>30 h</td>
</tr>
<tr>
<td>Theophylline</td>
<td>30</td>
<td>6.9</td>
<td>3.4</td>
<td>8.1 h</td>
</tr>
</tbody>
</table>
Theophyllin clearance according to age
PD-PK studies comparing different ages
(concentration-response data)

- Cyclosporin increased C-R < 4 years
- Midazolam decreased C-R < 29 weeks preterms
- Sotalol increased C-R in neonates
- Lanpoprazol increased C-R < 6 month
  (antisecretory effect)
- Ranitidine no difference in C-R (4-11 years)
- Bumetanide no difference (infants to young adults)

Reasonable to assume (pediatrics vs adults) similar disease progression? similar response to intervention?

NO

Conduct PK studies
Conduct safety
Conduct efficacy trials

YES TO BOTH

Reasonable to assume similar concentration-response (C-R) in pediatrics and adults?

NO

Is there a PD measurement that can be used to predict efficacy?

NO

YES

Conduct PK studies to achieve similar levels to adults
Conduct safety trials

Conduct PK/PD studies to get C-R for PD measurement
Conduct PK studies to achieve target concentrations based on C-R
Conduct safety trials

http://www.fda.gov/cder/mapp/4000.4.pdf
Examples for dose finding and clinical studies

Select the right patients – look for a valid endpoint

Examples:

- Antihypertensive agents
- Inhaled corticosteroids
Goal of antihypertensive clinical trials

- Extension of market exclusivity (patent extension)
- Pediatric labelling in the SPC
- Improved pediatric therapeutic arsenal
- Study goal: efficacy and safety:
  - positive dose-response
  - Superiority to placebo
  - interpretable results
Study designs A or B

A
- high
- medium
- low
- placebo

Pros
- Straightforward

Cons
- Recruitment difficult

B
- high
- medium
- low

Pros
- Simple

Cons
- Lack of control ADRs?
Study designs C or D

Dose titration

Pros

Placebo secondary

All children start with verum drug
Beta blockers


Bisoprolol/HCT

Randomization 1:2


Metoprolol

Study Design

<table>
<thead>
<tr>
<th>Screening</th>
<th>Titration</th>
<th>Maintenance</th>
<th>Tapering</th>
</tr>
</thead>
</table>

Weeks

Randomization

Placebo

0 2 4 6 8 10 12 14

D

A

2.0 mg/kg  2:
1.0 mg/kg  1:
0.2 mg/kg  2:
placebo    1

Universitätsklinikum Erlangen
**Bisoprolol/HCT**  

**Limitations**
Large placebo effect (34% < 90.Pc.)
Failure of most subjects to achieve BP control (45% < 90.Pc.)

Placebo n: 32, B/HTCT n: 62
Extended release Metoprolol

6-16 years
n: 114

**Systolic BP**

- Placebo (n=23) (n=45): -1.9
- 0.2 mg/kg (n=23): -5.2
- 1.0 mg/kg (n=49): -7.7
- 2.0 mg/kg (n=49): -6.3
- All active combined (n=117): -6.1

**Diastolic BP**

- Placebo (n=23) (n=45): -2.1
- 0.2 mg/kg (n=23): -3.1
- 1.0 mg/kg (n=49): -4.9
- 2.0 mg/kg (n=49): -7.5
- All active combined (n=117): -5.3

P-value vs. placebo:

- Systolic BP: 0.145, 0.027, 0.049, 0.035
- Diastolic BP: 0.655, 0.280, 0.017, 0.119
Summary so far..

- Only few young paediatric patients need a pharmacological treatment of arterial hypertension (renal diseases).
- Need also for children 2-5 years and infants and even for newborns.
- Only a limited number of patients are treated and therefore available for trials.
- For 2-5 years old, PK may be sufficient.
- Betablocker also used for cardiac arrhythmias and for prevention of migraine
Enalapril


after randomized washout
# Trials with antihypertensives and response to therapy

(age range 6 to 17 years, mean 12 years)

<table>
<thead>
<tr>
<th></th>
<th>amlodipine</th>
<th>enalapril</th>
<th>irbesartan</th>
<th>losartan</th>
</tr>
</thead>
<tbody>
<tr>
<td>End point</td>
<td>systolic</td>
<td>diastolic</td>
<td>systolic</td>
<td>diastolic</td>
</tr>
<tr>
<td>Success</td>
<td>negative</td>
<td>positive</td>
<td>negative</td>
<td>positive</td>
</tr>
<tr>
<td>Sample size</td>
<td>268</td>
<td>110</td>
<td>318</td>
<td>177</td>
</tr>
<tr>
<td>Dose range</td>
<td>2</td>
<td>32</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Dosing</td>
<td>low</td>
<td>medium</td>
<td>high</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 mg</td>
<td>5 mg</td>
<td>20 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.625 mg</td>
<td>2.5 mg</td>
<td>4.5 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt; 50 kg</td>
<td>&lt; 50 kg</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Benjamin DK et al. Hypertension 2008; 51: 834
Inhaled corticosteroids
Children aged between 1 and 4 years

- Discrepancy in the results of the dose-finding studies A and B and the validity of the endpoints (percentage of days with no cough and no wheeze).
  - Study A: **No statistically significant differences** were observed for the comparison of 50 µg twice daily or 100 µg twice daily with placebo for either endpoint.
  - Study B: **Statistically significant differences** were observed for the comparison of 100 µg twice daily or 250 µg twice daily with placebo for either endpoint.
- Subanalysis revealed that effects were present only in patients with chronic persistent moderate and severe asthma.
Inhaled corticosteroids
(select children with severe asthma to see the expected effects)

- Large studies with inhomogenous population
  (mild to moderate and severe asthma to allocate large numbers within a short period) are problematic.
- Lack of adequate efficacy data (dose-response, clinical endpoint) in the large group of patients studied
- Clear dose response in a subgroup of chronic persistent and severe asthma
- Conclusion: Select the right patients to see the effect
Paediatric Pharmacology – lessens learned

- PK is more variable, even within the pediatric population, than anticipated.
- Continued development of paediatric endpoints, assessment tools and even biomarkers.
- Trial designs are being modified as we learn from submitted studies.
Safety in published clinical trials
(Simmons HW: Acta paediatr 2008; 97:474)

- 739 trial in children
- 13 trial had safety monitoring committees (2%)
- 523 trials reported adverse events (AE) (71%)
- 151 of the AEs were serious (20%)
- 270 trial observed adverse drug reactions (ADR) (36,5 %)
- 80 of the ADR were moderate to severe (11%)
- 6 trial were terminated because of significant toxicity
- Death occurred in 83 trials, mostly unrelated to the drug (11%)
Safety within clinical trials is clearly defined, but.. The clinical trials per se will improve safety.

- Specific paediatric safety with respect to growth and development cannot be adequately addressed in a (short term) clinical trial for labeling. Separate long term pharmacovigilance procedures are necessary (e.g. reevaluation of study and control groups after years - restudy of the original cohort)

- Active surveillance during the study:
  SAE: Investigator immediately informs sponsor,
  Sponsor informs SUSAR to BfArM / EMEA, leading ethic committee and principal investigator.

- PSAR
- Pharmacovigilance
## Safety in clinical trials with antihypertensives

### number of reported paediatric AEs

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>placebo (n:685)</th>
<th>active (n:1022)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>3</td>
<td>1</td>
<td>0.19</td>
</tr>
<tr>
<td>Hypotension</td>
<td>0</td>
<td>3</td>
<td>0.13</td>
</tr>
<tr>
<td>Cardiac</td>
<td>8</td>
<td>16</td>
<td>0.50</td>
</tr>
<tr>
<td>Neuro/Psych.</td>
<td>13</td>
<td>26</td>
<td>0.48</td>
</tr>
<tr>
<td>Headache</td>
<td>113</td>
<td>179</td>
<td>0.68</td>
</tr>
<tr>
<td>Syncope</td>
<td>15</td>
<td>31</td>
<td>0.35</td>
</tr>
<tr>
<td>Gastrointest.</td>
<td>54</td>
<td>90</td>
<td>0.51</td>
</tr>
<tr>
<td>Asthma</td>
<td>11</td>
<td>12</td>
<td>0.58</td>
</tr>
<tr>
<td>Liver enzymes</td>
<td>7</td>
<td>7</td>
<td>0.51</td>
</tr>
<tr>
<td>Muscle aches</td>
<td>11</td>
<td>17</td>
<td>0.94</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>235</strong></td>
<td><strong>382</strong></td>
<td></td>
</tr>
</tbody>
</table>

Smith PB: Hypertension 2008; 51; 829
Safety in clinical trials with antihypertensives
number of SAEs

- Severe ADR
- Placebo transplantad rejection
- Ibesartan diabetic ketoacidosis
- Ibesartan syncopal event
- Lisinopril gastroenteritis
- Lisinopril pyuria

- None related to the drug

Smith PB: Hypertension 2008; 51; 829
Safety in clinical trials

Problems to be addressed

- No ADR or only frequent, well known ADR in a small group of paediatric patients (e.g. 6-12 years) does not mean the drug and the dose is safe for other ages.
- No clear information on rare or even new ADRs within the trial.
- Postmarketing surveillance is essential.
- Paediatric pharmacovigilance
- Use of trigger method to report signals or possible ADRs (age- and disease specific trigger tools).

A higher incidence of ADR with off-label use is probable.
Trigger-Tools

- Nosocomial infection
- Antibiotic use
- Accidental extubation
- Hypotension
- Respiratory arrest
- Death
- Catheter infections
- Naloxone
- Anticoagulant

- Rising serum creatinine
- Necrotising enterocolitis
- Seizures
- Phenobarbital
- Electrolyt abnormality
- Abnormal cranial imaging
- Hyperglycemia
- Re-Operation

Trigger-tools: Neonatal intensiv care unit

Safety issues
(clinical trials in children are conducted to improve safety)

- Adverse drug reactions (ADR) that are paediatric specific will not be defined without paediatric studies.
- Safety studies of sufficient duration and longer term follow-up studies remain problematic and cannot be addressed in short term drug approval clinical trial.
- I do not expect a higher incidence of ADR in children compared to adults, when clinical trials have been or are performed in adequate manner.
- Awareness that symptoms and signs or changes in disease state may be caused by the study drug(s)
- Active surveillance systems focusing on paediatrics studies in neonates and preematures
Summary

- Ethical issues have to be reassessed from the pediatric perspective e.g. it is unethical not to perform studies.
- The present incentive program still leaves many subpopulations unstudied.
- Clinical trials in children may require specific paediatric methodology and should be carried out by appropriately trained investigators.
- Continued development of pediatric endpoints and assessment tools.
- Better approaches to assess long term safety.
Thank you for your attention
# Experience from the USA

<table>
<thead>
<tr>
<th>Drug category of drugs studied in children</th>
<th>Most frequent drug classes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adults</td>
</tr>
<tr>
<td>CNS</td>
<td>CNS</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Alimentary tract</td>
<td>Alimentary tract</td>
</tr>
<tr>
<td>Antiifectives</td>
<td>Respiratory system</td>
</tr>
<tr>
<td>Antineoplastic agents</td>
<td>Antiifectives</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>Musculo-skeletal</td>
</tr>
<tr>
<td>Musculo-skeletal</td>
<td>Urogenital</td>
</tr>
<tr>
<td>others</td>
<td>others</td>
</tr>
</tbody>
</table>

*Boots et al, Eur J Pediatr 166:849, 2007*
Experience with paediatric labeling in the USA

- Incentives for the pharmaceutical industry since 10 years
  (6 month additional patent exclusivity)
- Drugs for adults were studied in children
- Specific paediatric medication have not yet studied sufficiently
  (rare indications?)
- Benefit for the pharmaceutical industry: 35 Mio US $ per drug

Dose selection
(optimal balance between clinical efficacy and safety)

- PK-PD studies (classical, population kinetics, modelling)
- Dose titration protocols?
- According to pharmacokinetic studies?
- Biomarkers
Dose selection in different age groups (optimal balance between clinical efficacy and safety)

- Adolescents  
  low adult dose
- Children 6 - 12 years  
  reduced doses as in off label
- Children 2 – 5 years  
  reduced doses as in off label
- Infants  
  weight adapted doses
- Neonates  
  rapid changes in drug deposition, special approaches
- Preterm infants