Evidence Generation in Neonates & Children

Hitish Pandya
Senior Lecturer
Paediatric Respiratory & HDU Medicine
University of Leicester
Evidence Generation in Neonates & Children

- ‘Regulatory’ approach to dose-finding – the reality
- The “Paediatrician’s approach” to dose-finding
- Potential solutions to a better landscape
Defining Drug Doses: Template by Regulators for Industry

Pediatric Study Decision Tree

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

NO

- Conduct PK studies
- Conduct safety/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?

YES

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

NO

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

YES

Guidance for Industry

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications
Blood Sampling Schedule for Phase 1 PK PD study in *children under 2* with acute respiratory distress
‘Regulatory’ PK-PD Study Designs - 2013

Blood Sampling Schedule for Phase 1 PK PD study in children under 2 with acute respiratory distress

Single- & Multiple- Dose Patients:

Pre study drug administration then post 2, 4, 8, 12, 24, 36, 48, 72, 96, 120 & 144 hours. On Day 5, if still hospitalized: pre-dose, 2, 4, 8, 12, 24 hours.

Altogether, up to 14 samples per patient
*Registered as a Phase 1 Unit

• Is this likely to be acceptable to any parent?
• Is it deliverable => how many children’s phase 1 units are there?

Impression:
Industry and Regulators ‘disconnected’ from patients and clinicians
Evidence Generation in Neonates & Children

“Dose selection” studies from the past & present
Corticosteroids for Chronic Lung Disease of Prematurity (CLD)

An Unstructured Drug Development “Program”
....a story of who, when, what and how much
Corticosteroids for CLD - "How much and how long"

Randomized placebo-controlled trial of a 42-day tapering course of dexamethasone to reduce the duration of ventilator dependency in very low birth weight infants: outcome of study participants at 1-year adjusted age

*Pediatrics 1999 Jul;104(1 Pt 1):15-21*

- *Dexamethasone Dose = 0.5 mg/kg/day*
- *Baby weight 0.5 - 1.5 Kg*
Corticosteroids for CLD - “When to start”

Prevention of chronic lung disease in preterm infants by early postnatal dexamethasone therapy.


Dexamethasone Dose = 0.5 mg/kg/day
Corticosteroids for CLD - “Inhaled or Oral CS ?”

A multicenter, randomized open study of early corticosteroid treatment (OSECT) in preterm infants with respiratory illness: comparison of early and late treatment with dexamethasone and inhaled budesonide


*Dexamethasone tapering course beginning with 0.5 mg/kg/day*

*Budesonide administered by MDI metered dose inhaler and spacer = dose of 400 microg/kg bd*
Corticosteroids for CLD
“How much – re-visited!”

Randomized controlled trial of three different doses of aerosol beclomethasone versus systemic dexamethasone to promote extubation in ventilated premature infants.

_Pediatr Pulmonol 2003;35(5):375-83._

Minidex: very low dose dexamethasone (0.05 g/kg/day) in chronic lung disease.

_Arch Dis Child Fetal Neonatal Ed 2011;96(3):F190-4._
CLD and Corticosteroids

Should and could we have taken a more sophisticated approach?
Corticosteroids for CLD

During all these *clinical trials* studies

No effort made to develop a PK-PD model for any corticosteroid in neonates

*No* rationale for dex dose of 0.5 mg/kg
(Dose for adults = 0.5 – 9.0 mg/day = 0.008 - 0.16 mg/kg)
Corticosteroids for CLD
Lack of Bio-analaytical Tools?

Still, no understanding of Dex blood levels in babies

*LC–MS chromatogram of an extracted dried blood spot (10 ul) collected from a preterm infant approximately 7 h following administration of a 50 μg/kg IV dexamethasone.*

Corticosteroids for CLD
Lack PD end-points?

Titrate steroid dose to known inflammatory biomarker?

- Role of elevated plasma soluble ICAM-1 and bronchial lavage fluid IL-8 levels as markers of chronic lung disease in premature infants.
  
  *Thorax. 1995 Oct;50(10):1073-9*

- Increase in the concentration of transforming growth factor beta-1 in bronchial lavage fluid before development of chronic lung disease of prematurity
  
Captopril – Another Case History

Captopril used to Px children with Heart Failure since early 1980’s

Adult dose for captopril based on PK-PD and clinical trial data involving patients with a variety of diseases incl. heart failure and hypertension

Note: ‘Paediatric’ heart failure is often not due to diseases linked to heart failure in adults
Captopril & Heart failure

Observational “drug-dosing” study of Captopril in children with heart disease

Captopril in treatment of infant heart failure: a preliminary report:
Captopril dose: “up to 3.5 mg/kg/day (mean 2.47 mg/kg/day)”
N= 18 patients

Int J Cardiol. 1987;16(3):295-301

No other studies
Current dose range in children - 0.3 to 1.5 mg/kg
Captopril & Heart failure

- Child dose = 0.3 to 1.5 mg/kg
- Adult dose = 100-150 mg/day, ~ 1.4 – 2mg/kg (70kg adult*)
- Adults dosing based on licensed tablet
- Children dose based on an unlicensed liquid formulation
Captopril & Heart failure -
How confident can we about the drug and drug dose?

(a) Captopril not stable in solution
Variations in captopril formulations used to treat children with heart failure: a survey in the UK

Mulla H, Tofeig M, Bu'Lock F, Samani N, Pandya HC. Arch Dis Child. 2007

(b) Liquid captopril not bioequivalent to tablet
Assessment of liquid captopril formulations used in children.

Mulla H, Samani NJ, Pandya HC. Arch Dis Child. 2011
Do (UK) Paediatricians see a need for dose finding studies?

Defining Captopril PK-PD in Children with heart disease
(Using clinical parameters, Renin & Angiotensin levels as PD endpoints)

Submitted to “The first HTA-themed call covering “medicines for children” in 2006

Rejected => Chair of HTA
“We don’t fund PK-PD studies”
Do Paediatricians see a need for dose finding studies?

“MAGNETIC Study”
funded at the first HTA themed call covering on “medicines for children” in 2006

MAGNEsium for Acute Severe Asthma
A phase 3 study

Note: Mg$^{2+}$ not licensed in children or adults for asthma
Do Paediatricians see a need for dose finding studies?

Cochrane review of $\text{Mg}^{2+}$ in Asthma (2000)

(Paediatricians in review team)

$\Rightarrow$

Conclusion .......“Need to perform dose finding studies”
Do Paediatricians see a need for dose finding studies?

‘MAGNETIC’ = **Nebulised** Mag for children with *mild asthma* attack

NO prior dose finding studies

Centres allowed to use any nebuliser device available
Drug Delivery and Nebulisers

Testing of nebulizers for delivering magnesium sulfate to pediatric asthma patients in the emergency department. Respir Care. 2011 Mar;56(3):314-8

“In preparation for a canadian multicentre study of inh Mg in asthmatic children ....we conducted a study to choose the best nebulizer system”

RESULTS:

• The Pari LC Star had an appropriate particle size distribution but a very slow aerosol output rate.

• The Omron MicroAir had an even slower output rate and a larger particle size distribution, which would be inappropriate for smaller children.

• In vitro lung deposition with the Aeroneb Go with Idehaler was 16.0 ± 0.4 mg/min in older children and approximately a fifth of that in toddlers
‘MAGNETIC’ - Success or Failure?

Methods MAGNETIC was a double blind randomised placebo-controlled study in an acute paediatric setting. Children aged between 2 and 16 years with acute severe asthma (as defined by the BTS) were treated with standard care of a combination of three doses of nebulised salbutamol and ipratropium bromide and in addition were randomised to receive either nebulised magnesium or placebo every twenty minutes for the first hour. Primary outcome was the asthma severity score (ASS; score 0-9) at 60 minutes post treatment. Secondary outcomes were length of stay (LOS), need for intravenous bronchodilator treatment (IV), need for intensive care admission (PICU) or intubation, number of additional salbutamol administrations whilst in hospital and adverse events.

Results 508 children (median age 4.0 years; 58% males) were recruited from 30 centres. 252 children received nebulised magnesium and 256 children received placebo. There were no important clinical differences in baseline characteristics (table 1).

Using ANCOVA regression those children with the shortest duration of attack showed the greatest response (difference in deviance=6.86 on 2 df, p=0.02 estimate -0.79 (-1.59, -0.03)) (table 2).

Conclusion Nebulised magnesium has a significant effect on the asthma severity score at one hour post initial treatment. This effect is most marked in those children who have the shortest duration of exacerbation at presentation.

Study deemed “a success” for UK MCRN

Are we confident in rejecting / accepting the null hypothesis?
Connecting Industry, Regulators & Clinicians
Dried blood spots and sparse sampling: a practical approach to estimating pharmacokinetic parameters of caffeine in preterm infants

Parul Patel,1 Hussain Mulla,1 Venkatesh Kairamkonda,2 Nell Spooner,3 S Gade,3 Oscar Della Paqua,4 David J. Field2,5 & Hitesh C. Pandya1,6

1Centre for Therapeutic Evaluation of Drugs in Children, Glenfield Hospital, Leicester. 2Neonatal Intensive Care Unit, Leicester Royal Infirmary, Leicester. 3Platform Technologies and Science Drug Metabolism and Pharmacokinetics, GlaxoSmithKline, Ware. 4Clinical Pharmacology & Discovery Medicine, GlaxoSmithKline, Greenford. 5Department of Health Sciences, University of Leicester, Leicester and 6Department of Infection, Immunity and Inflammation, University of Leicester, Leicester, UK

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT
Recruitment & Samples

• N = 67 neonates, Birth weight = 0.6 – 2.11 kg; Gestation 25-32 weeks; only 5 parents refused

• Maximum blood volume taken 480 µl

• Median Nos DBS samples (time points) / baby ~5

• In total 384 DBS samples were received and 344 results were issued
Bioanalytical Findings
Wednesday 9th February 2011

Laboratory Assessment of “real-life” micro-volume samples
Incurred Samples Analysis

- ISR has previously been reported on Caffeine DBS from adult clinical study
- 3.1% of total study samples were reanalyzed. No Incurred results were outside the limits of +/- 20% of the mean of the reanalysis result and its corresponding original result. The results confirm bioanalytical reproducibility in incurred Human Blood Spot samples containing Caffeine.
Haematocrit Assessment

- Concentrations assessed 1000 ng/mL and 20000 ng/mL
- HCT was adjusted by adding (reduces HCT) or removing (increases HCT) plasma from whole blood
- HCT was assessed at 6 levels down to 0.2 (20%) which was the lowest level observed in the first shipment of samples, highest observed 0.5
- Normal HCT ranges from:
  - Adult females 36 – 48
  - Adult Males 40 – 52
  - Neonates 28 – 67
- A strong negative bias was observed with decreasing HCT
- GSK have previously reported a strong positive bias with increasing HCT, difference (%) from 0.45:
  - 0.55 = 21.0
  - 0.65 = 42.3

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Mean Peak Area Ratio</th>
<th>Standard Deviation</th>
<th>CV (%)</th>
<th>% Difference from 0.45 HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT (0.20) n = 6</td>
<td>0.135</td>
<td>0.005</td>
<td>3.41</td>
<td>-33.42</td>
</tr>
<tr>
<td>HCT (0.25) n = 6</td>
<td>0.134</td>
<td>0.005</td>
<td>3.81</td>
<td>-33.93</td>
</tr>
<tr>
<td>HCT (0.30) n = 6</td>
<td>0.139</td>
<td>0.004</td>
<td>3.05</td>
<td>-31.40</td>
</tr>
<tr>
<td>HCT (0.35) n = 6</td>
<td>0.151</td>
<td>0.007</td>
<td>4.70</td>
<td>-25.20</td>
</tr>
<tr>
<td>HCT (0.40) n = 6</td>
<td>0.165</td>
<td>0.011</td>
<td>6.84</td>
<td>-18.37</td>
</tr>
<tr>
<td>HCT (0.45) n = 6</td>
<td>0.202</td>
<td>0.011</td>
<td>5.61</td>
<td>0.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Mean Peak Area Ratio</th>
<th>Standard Deviation</th>
<th>CV (%)</th>
<th>% Difference from 0.45 HCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCT (0.55) n = 6</td>
<td>1.250</td>
<td>0.07</td>
<td>5.43</td>
<td>21.0</td>
</tr>
<tr>
<td>HCT (0.65) n = 6</td>
<td>1.470</td>
<td>0.05</td>
<td>3.60</td>
<td>42.3</td>
</tr>
</tbody>
</table>
Petroleum Jelly Assessment

- Petroleum jelly was used on the heel to help form a blood droplet, a practice not used for GSK DBS clinical studies.

- Concentrations assessed 1000 ng/mL and 20000 ng/mL.

- A thin layer of petroleum jelly was placed on a glass slide. 30µL droplets of blood spiked with caffeine were placed on the slides left for 1 and 10 minutes, 15µL was then spotted on to Whatman FTA Elute cards.

- The process was repeated using glass slides without petroleum jelly.

- The difference between samples exposed to petroleum jelly and those not is minimal. Therefore its use is not thought to affect the sample analysis.

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Mean Peak Area Ratio</th>
<th>SD</th>
<th>CV (%)</th>
<th>% Difference from (-) at 1 minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-) 1 minute n=6</td>
<td>0.741</td>
<td>0.053</td>
<td>7.21</td>
<td>0.00</td>
</tr>
<tr>
<td>(+) 1 minute n=6</td>
<td>0.733</td>
<td>0.053</td>
<td>7.27</td>
<td>-1.02</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sample Name</th>
<th>Mean Peak Area Ratio</th>
<th>SD</th>
<th>CV (%)</th>
<th>% Difference from (-) at 10 minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-) 10 minutes n=6</td>
<td>0.724</td>
<td>0.055</td>
<td>7.59</td>
<td>0.00</td>
</tr>
<tr>
<td>(+) 10 minutes n=6</td>
<td>0.786</td>
<td>0.039</td>
<td>5.01</td>
<td>8.58</td>
</tr>
</tbody>
</table>
Patient & Staff Views: DBS and Sparse Sampling

“I thought there was something I wasn’t reading, because it was so straightforward... was there something...between the lines?” (M22)

• Staff felt informed and understood project
• Nurses participated (taking samples, reminding doctors)
• Didn’t disrupt normal working patterns, or generate too much paperwork!
• Involved nurses that don’t normally see research

“we did lose a baby at twenty-one weeks last year. ... and we had the post-mortem, and they were talking about doing the research about different things. And I didn’t want his life to be, you know, sort-of in vain” (M78)
Co-development & Evaluation of PK-PD Platforms

Protocol Co-development Involved
• Bioanalysts
• PK-PD Modellers
• Paediatricians

Study co-funded by UoL and GSK
Not sustainable
How do we connect with each other, sustainably?

Improve ‘Market’ Conditions?

(i) ‘Stick’
Justify absence of PK-PD data in CTA application for a phase 3 study

Justify rich sampling, macro-volume approach in CTA application in PK-PD studies

(ii) ‘Carrot’
Sustained support for Academic Paediatric PK-PD groups
Questions?