PK-PD Dosing Issues in Special Patient Populations

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ST GEORGE’S UNIVERSITY LONDON
PK-PD Dosing Issues in Special Patient Populations

“Not Miniature Men and Women”
Abraham Jacobi

Contains 12% of alcohol by weight or 14% per volume. Use as a solvent.

DIRECTIONS:
For adults: Take a teaspoonful about one-half hour before meals and when retiring.

For children: Half dose. If the taste is not liked, it may be combined with a mouthful of water.
Factors that influence tissue drug concentrations over time include Absorption, Distribution, Metabolism and Excretion (ADME). (Formulation!)

These ADME processes differ in *neonates, children, pregnancy and elderly* populations with major consequences on the pharmacokinetic profile of a drug.

High VARIABILITY in ADME have direct effect on antibiotic PK/PD – concern especially in older drugs with a narrow therapeutic index.

PK-PD Dosing Issues in Special Patient Populations

• Neonates and children
• Pregnancy
• Elderly
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The continuous development

- Preterm newborn
- Newborn (0–28 days)
- Infant (>28 days–12 months)
- Toddler (>12 months–23 months)
- Preschool child (2–5 years)
- School age child (6–11 years)
- Adolescents (12–18 years)

Many physiological changes take place during childhood which may have an impact on the pharmacokinetics and dynamics of a compound.

International Conference on Harmonization (ICH) E11 classifications
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Changes in Antimicrobial pharmacokinetics with age

Source: Dr Saye Khoo, Liverpool
## PK-PD Dosing Issues in Special Patient Populations

### Children and neonates

<table>
<thead>
<tr>
<th>Developmental change</th>
<th>PK consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓Gastric pH</td>
<td>↑(C_{\text{max}}) for weak acids</td>
</tr>
<tr>
<td>↓Intestinal transit</td>
<td>↓(C_{\text{max}}) and ↓AUC</td>
</tr>
<tr>
<td>↓Intestinal bile concentration</td>
<td>↓(C_{\text{max}}) and ↓AUC</td>
</tr>
</tbody>
</table>

### Absorption

<table>
<thead>
<tr>
<th>Physiological factor</th>
<th>Newborn (full-term)</th>
<th>Neonate (1 day–1 month)</th>
<th>Infant (1 month–2 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric pH</td>
<td>1–3</td>
<td>&gt;5</td>
<td>~Adult</td>
</tr>
<tr>
<td>Gastric emptying time</td>
<td>Reduced (variable)</td>
<td>Reduced (variable)</td>
<td>Increased</td>
</tr>
<tr>
<td>Intestinal surface area</td>
<td>Reduced(^a)</td>
<td>Reduced(^b)</td>
<td>~Adult</td>
</tr>
<tr>
<td>Intestinal transit time</td>
<td>Reduced</td>
<td>Reduced</td>
<td>Increased</td>
</tr>
<tr>
<td>Pancreatic and biliary function</td>
<td>Very immature</td>
<td>Immature</td>
<td>~Adult</td>
</tr>
<tr>
<td>Bacterial flora</td>
<td>Very immature</td>
<td>Immature</td>
<td>Immature</td>
</tr>
<tr>
<td>Enzyme/transporter activity</td>
<td>Very immature</td>
<td>Immature</td>
<td>Approaching adult</td>
</tr>
</tbody>
</table>
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Children and neonates

Comparison of serum levels following the administration of oral and parenteral preparations of penicillin to infants and children of various age groups

This higher pH in neonates and young infants may have a protective effect on acid-labile drugs and may at least partially account for the higher bioavailability of beta-lactam antibiotics.

(Huang et al, J paediatrics 1953)
### PK-PD Dosing Issues in Special Patient Populations

#### Children and neonates

<table>
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<tr>
<th>Developmental change</th>
<th>PK consequence</th>
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</thead>
<tbody>
<tr>
<td>Body composition</td>
<td>⇔ $V_d$</td>
</tr>
<tr>
<td>• neonates have relatively reduced fat</td>
<td></td>
</tr>
<tr>
<td>• infants have increased fat compared with adults</td>
<td></td>
</tr>
<tr>
<td>• extracellular water is relatively higher in neonates – Immature blood brain barrier</td>
<td></td>
</tr>
</tbody>
</table>

↓ plasma protein  
↑ free fraction of drug in plasma  
↑ $V_d$

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Neonate</th>
<th>Infant</th>
<th>Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total protein</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Plasma albumin</td>
<td>Decreased</td>
<td>Equivalent</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Plasma globulin</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Equivalent</td>
</tr>
<tr>
<td>$\alpha_1$-acid glycoprotein</td>
<td>Decreased</td>
<td>No data available</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Free fatty acids</td>
<td>Increased</td>
<td>Equivalent</td>
<td>Equivalent</td>
</tr>
<tr>
<td>Unconjugated bilirubin</td>
<td>Increased</td>
<td>Equivalent</td>
<td>Equivalent</td>
</tr>
</tbody>
</table>
# PK-PD Dosing Issues in Special Patient Populations

## Children and neonates

### Metabolism

<table>
<thead>
<tr>
<th>Developmental change</th>
<th>PK consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic metabolism</td>
<td></td>
</tr>
<tr>
<td>Phase I enzyme activity</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>Hepatic clearance</td>
</tr>
<tr>
<td>Hepatic metabolism</td>
<td></td>
</tr>
<tr>
<td>Phase II UGT enzyme activity</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>Hepatic clearance</td>
</tr>
<tr>
<td>Bacterial colonization of the intestine</td>
<td>↑C(_{\text{max}}) and ↑AUC</td>
</tr>
</tbody>
</table>

### Graph

- **Y-axis:** Enzyme activity ratio to adult mean value
- **X-axis:** Developmental groups
- **Categories:** Fetus, <24 hours, 1-7 days, 8-28 days, 1-3 months, 3-12 months, Adults
- **Legend:**
  - CYP1A2
  - CYP2C9
  - CYP2C19
  - CYP2D6
  - CYP2E1
  - CYP3A4
Excretion of drugs by the kidneys is dependent on three processes, glomerular filtration (GFR), tubular secretion and reabsorption (TS/R) (colistin high TR). They are dependent on renal blood and renal plasma flow $Q$, which increase with age as a result of an increase in cardiac output and a reduction in peripheral vascular resistance.
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Dosing of oral penicillins in children: is big child=half an adult, small child=half a big child, baby=half a small child still the best we can do? Ahmed U et al, BMJ 2011
### PK methods: why population PK?

<table>
<thead>
<tr>
<th>Traditional PK</th>
<th>Population PK studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rich sampling</td>
<td>Sparse sampling</td>
</tr>
<tr>
<td>Ethical issues</td>
<td>Between subject variability</td>
</tr>
<tr>
<td>Practical challenges</td>
<td>Explain drug disposition</td>
</tr>
<tr>
<td>Recruitment issues</td>
<td>Modelling and simulation (M&amp;S)</td>
</tr>
<tr>
<td>Generalisability varies</td>
<td>Now standard in paediatrics</td>
</tr>
</tbody>
</table>
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Challenges to studies with children and neonates

Neonatal and Paediatric Pharmacokinetics of Antimicrobials Study

- Recruited **216 neonates and 212 children**
- PopPK successfully integrated into routine care
- Opportunistic (and optimal) sampling strategies
- Methods feasible in NHS setting

An open label, multicenter, pan-European, randomised active-comparator controlled phase III superiority trial

- European multicenter network to evaluate pharmacokinetics, safety and efficacy of Meropenem in neonatal sepsis and meningitis
- Recruited **272 neonates**

NeoVanc-1- Hollow fibre infection and rabbit models

NeoVanc-2 - Population PK meta-analysis of previous neonatal, vancomycin pharmacokinetics data

NeoVanc-3 Open label European, multi-centre, Phase IIb, randomised, active control, parallel group, non-inferiority trial

- Compare the efficacy, safety and pharmacokinetics of an optimised dosing to a standard dosing regimen of vancomycin
- **300 participants** is planned to be enrolled from five EU countries
PK-PD Dosing Issues in Special Patient Populations

- Children and neonates
- Pregnancy
- Elderly
PK-PD Dosing Issues in Special Patient Populations

**Pregnancy (maternal sepsis)**

**Change in Pregnancy**
- ↓ gastric acidity
- Slower gastric emptying
- ↑ Increased oro-cecal transit time in third trimester

**Change in Pregnancy**
- ↑ Plasma volume
- ↓ Albuminemia
- ↑ Hepatic blood flow
- Changes to regional blood flow
- ↓ serum creatinine and urea
- ↑ activity of renin-angiotensin system

**Change in Pregnancy**
- Cardiac output ↑ 30%-50%
- ↑ Respiration rate
- ↑ in stroke volume and heart rate
- ↓ functional reserve capacity
- GFR ↑ 50%

**Change in Pregnancy**
- Increased levels of estrogen and progesterone modulate enzymatic: CYP P450 activity which can be ↑ (ie, CP3A and CYP2A6) or ↓ (ie, CYP1A2)
- Increased hepatic blood flow
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A European clinical pharmacology network to investigate the Pharmacokinetics of ANtiretroviral agents in HIV-infected pregNANt women

• Was almost no data on ARVs in pregnancy – critical to optimise dosing to reduce MTCT

• PENTA network developed for PK of mothers taking ARVs in pregnancy

• Combination antiretroviral treatment (cART): 2 NRTI’s and integrase inhibitor, protease inhibitor/r, or NNRTI now have optimal doses

• Could be adapted for antimicrobials
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Feasible

The pharmacokinetics, safety and efficacy of tenofovir and emtricitabine in HIV-1-infected pregnant women

*AIDS* 2013, 27:739–748

Maraviroc Pharmacokinetics in HIV-1–Infected Pregnant Women

*CID* 2015:61 (15 November)

Raltegravir in HIV-1–Infected Pregnant Women: Pharmacokinetics, Safety, and Efficacy

*HIV/AIDS* • *CID* 2015:61 (1 September)

Pharmacokinetics of total and unbound darunavir in HIV-1-infected pregnant women

*J. Antimicrob Chemother* 2015; 70:534–542

First reported use of elvitegravir and cobicistat during pregnancy

*AIDS* 2016, 30:807–812
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• Children and neonates
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• Elderly
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Elderly
(dose adjustment, toxicity, polypharmacy)

Change in elderly

- ↓ gastric acidity
- ↓ due to certain comorbidities (e.g., diabetes, Parkinson’s Disease) and certain medications (e.g., anticholinergics and opioids)

- ↓ muscle mass
- ↓ body fat
- ↓ total body water

- ↓ in plasma albumin (further reduction may be due to age-related chronic conditions)
a1-acid glycoprotein may be increased (due to acute illness or chronic inflammatory disease states)

- ↓ first-pass metabolism due to reduced liver blood flow and mass

- ↓ renal function is common in older adults
- ↓ in stroke volume and heart rate
- ↓ functional reserve capacity
- ↓ GFR

Change in elderly

- Metabolizing capacity, PHASE 1: mostly due to reduced hepatic blood flow and mass and reduced oxygen availability
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THE FUTURE

PK STUDIES of NEW AB for the PAEDIATRIC POPULATION

- **Populations to cover and age groups:**
  
  a. 12-18 years
  
  b. 2-11 years (could be divided into 2-5 years and 6-11 years)
  
  c. PMA >44 weeks to 2 years
  
  d. PMA <44 weeks (important to include VLBW and ELBW)

  studies from 2-18 years could be conducted in parallel

- **Study design:**
  
  - Sample size justified according to expected variability in PK using adult and or PBPK extrapolation – POSSIBLY ONLY SINGLE/MULTIPLE DOSE PK.
    
    a. 7-9 evaluable patients per age cohort is usually the minimum requirement
    
    b. 50 time-points at different times are needed in sparse sampling studies

- **Data analysis:**
  
  - Population PK models should be developed first from adult data to support extrapolation, and then updated to cover all studied paediatric age groups
  
  - Probability of target attainment (PTA) should be simulated for all age groups – RE-CONSIDER PD TARGETS IN SPECIAL POPULATIONS...
PK-PD Dosing Issues in Special Patient Populations

NeoAMR
## PK-PD Dosing Issues in Special Patient Populations

### Indication
Empiric treatment of neonatal sepsis, including meningitis (premature and term, early and late onset)

### Patient Population
Neonates with pSBI in settings of high prevalence of resistance to first line WHO empiric therapy

### Route of Administration
i.v. (intravenous), 30-120 min infusions

### Dosing Schedule
2-4 x daily

### Efficacy
Comparable clinical activity to amoxicillin/gentamicin or ceftriaxone/gentamicin in claimed indication

Clinical activity in pathogens resistant to amoxicillin/gentamicin or ceftriaxone/gentamicin

### Treatment duration
5-28 days

### Safety / Tolerability
Low propensity for resistance development, large therapeutic window concerning hepatotoxicity, nephro- and CNS-toxicity, no QT-prolongation

### Drug Interactions
Comparable to competitors

### Key Countries
Europe, the Americas, Asia, Africa

### Price / Day of Therapy
Average ex-factory price at launch: low/DOT (directly observed therapy)

### Pharmacoeconomics
Reduction of intensive care unit and hospitalization days (modelling). Reimbursable
PK-PD Dosing Issues in Special Patient Populations

NeoFosfo

Objectives
- assess the safety of IV fosfomycin with regard to possible elevation of sodium, calcium and creatinine at Day 2 and 7 in neonates
- estimate the PK of IV fosfomycin in neonates
- estimate the oral bioavailability of fosfomycin in neonates

Treatment
Randomised to Amp/Gent (SoC) vs Amp/Gent plus a 7-day course of fosfomycin
48 hours (or more) IV fosfomycin, followed by up to 5 days of oral fosfomycin.
Neonates will move to oral fosfomycin once they are tolerating oral feeds.

PK and Safety Sampling
- Two PK samples will be taken after the first IV and oral doses; the sampling times will be randomly allocated to one of three possible early and late time points
- blood sampling for electrolytes including sodium at Day 2 and 7 to assess fosfomycin safety

Statistics
Sample size: 60 babies to get 45 with complete PK
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<td>Neonatal sepsis, where MDR Gram-negative pathogens have been demonstrated, including <em>K. pneumoniae</em>, <em>P. aeruginosa</em> or <em>Acinetobacter spp.</em> Including CROs</td>
</tr>
<tr>
<td><strong>Patient Population</strong></td>
</tr>
<tr>
<td>Hospitalized neonates with severe infections, failure on optimal current treatment and proven microbiology</td>
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<td><strong>Route of Administration</strong></td>
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<tr>
<td><strong>Efficacy</strong></td>
</tr>
<tr>
<td>Comparable clinical activity to existing options in claimed indication</td>
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<tr>
<td><strong>Clinical activity in pathogens resistant to carbapenems</strong></td>
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<tr>
<td><strong>Treatment duration</strong></td>
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<td><strong>Pharmacoeconomics</strong></td>
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<td>Reduction of intensive care unit and hospitalization days (modelling). Reimbursable</td>
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<td><strong>Main Competitors</strong></td>
</tr>
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<td>Colistin monotherapy</td>
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PK-PD Dosing Issues in Special Patient Populations

OPTIONS FOR IMPROVING THE PHARMACOVIGILANCE OF NEONATAL AND PAEDIATRIC AB POST MARKETING APPROVAL

• The reporting of pharmacovigilance data on antibiotics in neonates and children is currently limited.

• PENTA has collected extensive PV data through the establishment of a European Pediatric Registry – EPPICC.

• A similar approach could use a Sentinel Survey approach in a network of major children’s hospitals, collecting clinical, safety and outcome data on children prescribed specific ABs.

• Post Marketing Authorisation registry data should become an increasingly important component of Pediatric AB DD programs
PK PD IN SPECIAL POPULATIONS

• High unmet clinical need – 2 billion children – quarter global population – 130 million newborns
• Complex PK, but improved study design, M+S, make studies much more feasible
• Continuing need to accelerate studies of new AB...continued pragmatism required – some data better than no data..including neonatal PK
• Major programme to define optimal old AB combinations for MDR infections in pregnancy, neonates and children – GARDP
  • Further consideration about PD in special populations..
• Manage risk – inaction is not an option