Scaling pharmacodynamics in children: Lessons from immunology, infectious diseases and critical care

Joe Standing

j.standing@ucl.ac.uk

MRC Fellow: UCL Great Ormond Street Institute of Child Health
Antimicrobial Pharmacist: Great Ormond Street Hospital for Children
Honorary Senior Lecturer: St George’s University of London

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Data for today:

Prospective clinical trials, e.g.:
  ▶ NeoMero
  ▶ Treosulfan PKPD myeloablative stem cell transplant conditioning
  ▶ Dexmedetomidine sedation
  ▶ (PENTA network HIV studies)

Retrospective cohort studies (prospective evaluation sometimes):
  ▶ From the GOSH “data lake”
Great Ormond Street Hospital (GOSH) data lake:

- B-cell suppression with rituximab in rheumatology
- Immune reconstitution post stem-cell transplant
- Antimicrobial PKPD studies
Scaling pharmacodynamics in children

- pre-term neonate (born before 37 weeks)
- neonate (age < 1 month)
- infant (age 1 month to < 2 years)
- child (age ≥ 2 to < 12 years)
- adolescent (age ≥ 12 to < 18 years)
- adult (age ≥ 18 years)

gestational age + post natal age = post menstrual age
Definition 2

Scaling **pharmacodynamics in children**

- measured response to drug, and how evolves with time
- pharmacokinetics drives pharmacodynamics

General question:

- How to choose the PK endpoint $C(t), C_{max}, C_{min}, AUC$?
- What is the pharmacological rationale?
Definition 3

Scaling pharmacodynamics in children

- i.e. can we predict PD in children knowing adult PD?

What do paediatricians say?
- Children are not small adults

What do we say?
- Agree (since Child \( \notin \) Adult - see Definition 1 slide)
Aside: Turns out paediatricians are small adults (Tabner 2016):

Does repeating “children are not small adults” get us anywhere?
History lesson: Scaling PK

Regulatory changes $\rightarrow$ ↑ PK studies from early 2000s

QUIZ

- Who first suggested CL may not scale per kg?

Clue 1:
- Surname ends in “_ _ _ ford”

Clue 2:
- Suggested link with allometric metabolic rate scaling
ANSWER:

- Crawford Pediatrics 1950:

SIMPLIFICATION OF DRUG DOSAGE CALCULATION BY APPLICATION OF THE SURFACE AREA PRINCIPLE

*By John D. Crawford, M.D., Mary E. Terry and G. Margaret Rourke*

*Boston*
Is “Crawford” the 1950 pseudonym for a small adult named “Holford”?
Lamivudine, Burger 2007

- 4 year old CL ≈ 1 L/h/kg
- 12 year old CL ≈ 0.5 L/h/kg
- These PK studies changed ART dosing, why???

Underdosing of antiretrovirals in UK and Irish children with HIV as an example of problems in prescribing medicines to children, 1997-2005: cohort study

Ese N Menson, A Sarah Walker, Mike Sharland, Carole Wells, Gareth Tudor-Williams, F Andrew I Riordan, E G Hermione Lyall, Diana M Gibb, for the collaborative HIV paediatric study steering committee
Dapsone, Gatti 1995

![Graphs showing the relationship between age and height vs. CI/F and CL/F](image)
Carboplatin, Veal 2010
Figure 1. IBVU clearance by age group. Comparison of final clear-
Busulfan, Hassan 2002

Cl = 3.68 - 0.028 × age
r = 0.896, P < 0.001

Cl = 91.2 - 0.02 × age
r = 0.02, P = 0.91
Omeprazole, Marier 2004

![Graph showing CL/F (L/h/kg) vs Age (y)](image_url)

- $r^2 = 0.0729, p = \text{NS}$
- $r^2 = 0.0252, p = \text{NS}$
Gabapentin, Haig 2001
Zidovudine, Fillekes 2014

The graph shows the relationship between age (years) and Zidovudine clearance (L/h/kg). The regression line and confidence interval are depicted with a p-value of <0.001 adjusted for dose and weight-for-age.
Ketobemidone, Lundeberg 2009

![Graph showing clearance (L/hour/kg) vs age (days and years) for different groups.](image-url)
Allometry, Shallometry!

Dennis M. Fisher, MD,* and Steven L. Shafer, MD†

We have biological prior information ...
CL scaling

Biological “priors” on PK scaling:

▶ liver size scales with weight$^{0.78}$ (Johnson 2005)
▶ glomerular filtration scales with weight$^{0.63}$ (Rhodin 2009)
▶ understanding maturation: e.g. Upreti 2016 shows how; Calvier 2017 explores why (with PBPK):

Meta-Analysis of Hepatic Cytochrome P450 Ontogeny to Underwrite the Prediction of Pediatric Pharmacokinetics Using Physiologically Based Pharmacokinetic Modeling

Vijay V. Upreti, PhD, FCP$^1$ and Jan L. Wahlstrom, PhD$^2$

Allometric Scaling of Clearance in Paediatric Patients: When Does the Magic of 0.75 Fade?

Elisa A. M. Calvier$^1$ · Elke H. J. Kreckels$^1$ · Pyry A. J. Väätelä$^1$ · Amin Rostami-Hodjegan$^1$ · Dick Tilbøe$^3$ · Meindert Danhof$^4$ · Cathérine A. J. Kuibe$^{1,4}$
Volume (generally) linear (Price 2003)

Busulfan, Hassan 2002

Ketobemidone, Lundeberg 2009

Oxaliplatin, Nikanjam 2015

Dapsone, Gatti 1995 (not always)
PK scaling theory
PK scaling reality (treosulfan)
What about pharmacodynamics?

- PD endpoints heterogeneous and lack of standards for a valid/reliable
- Crisis in paediatric drug development: e.g. 42% failure rate in 1998-2012
- Matching PK exposure does fail: e.g. 50% of anti-hypertensive trials
- Plenty of biological/clinical priors e.g. Vaccines, epilepsy:
Overview

Pharmacodynamic scaling in children:

- Introduction
- Lessons from anaesthesia/analgesia
- Lessons from immunology
- Lessons from infectious diseases
- Conclusions
PD scaling of morphine in post-operative pain

Definition:

▶ “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

Biological prior:

▶ Possible down regulation of $\mu$-opioid receptor in neonates (rat data)

Scaling question:

▶ Do neonates need lower than expected morphine doses?
PD scaling of morphine in post-operative pain

Hypothesis:
▶ Morphine dosing will follow PK maturation/allometric scaling

Data:
▶ GOSH pain registry (1996–), > 35000 episodes, prospective data capture (iPads)
▶ Choose < 6 year olds, on morphine infusion and paracetamol only, hourly morphine dose sum of background rate and boluses

Methods:
▶ PK model: as $t \to \infty$, $C(t) = \frac{r}{CL}$, where $r$ is the dose rate
▶ if analgesic effect $\propto C(t)$ then $r \propto CL$
▶ for 2–6 year olds fitting $\log(r) = \beta \log(wt) + \alpha$, $\hat{\beta} = 0.79$ i.e. follows allometry
▶ Now fit: $r \left( \frac{70}{wt} \right)^{0.75} = R \frac{pma^\gamma}{pma^\gamma + PM_{50}^\gamma}$, where $R$ is mature rate, $PM_{50}$, value of half mature post menstrual age:
PD scaling of morphine in post-operative pain

Blue: data fit

Similar to PK maturation
Anderson 2011
PD scaling of dexmedetomidine sedation

Measuring sedation:
- Algorithms for EEG interpretation inappropriate in neonates/infants?

Biological prior: location of $\alpha_2$ determines excitatory or inhibitory effect:

Scaling question:
- Since dexmedetomidine’s sedative effects are largely agonism in the locus coeruleus expect no age scaling
Hypothesis:
- Dexmedetomidine PD will scale with known PK maturation/allometric scaling

Data:
- Prospective clinical study of dexmedetomidine for MRI sedation
- 53 patients, 428 sedation measurements (1-5 scale)
- Ordered categorical model with first-order Markov

Method:
- Look at whether/how $E_{max}$ scales with age
PD scaling of dexmedetomidine sedation

▶ weak age effect, but not seen in:

*High dose dexmedetomidine as the sole sedative for pediatric MRI*

KEIRA P. MASON MD†, DAVID ZURAKOWSKI PhD*†, STEVEN E. ZGLESZEWSKI MD*, CAROLINE D. ROBSON MB, CHB†, MAUREEN CARRIER RN, BSN†, PAUL R. HICKEY
PD scaling of myeloablation

Biomarker:
- Very clear, measured in routine full blood count

Biological prior:
- Normal neutrophil counts do not radically change with age
- Allometric principles suggest dynamics faster in smaller individuals

Scaling question:
- Does drug-induced myeloablation require age scaling?
PD scaling of myeloablation

Hypothesis:
▶ Drug-induced myeloablation in haematopoietic stem cell transplant (HSCT) does not change with age

Data:
▶ Prospective Phase II study of treosulfan conditioning
▶ 84 patients, ≥ 6 months follow-up
▶ Treosulfan PK, daily full blood counts, long-term engraftment measures in myeloid cells

Method:
▶ Use Friberg model for short-term reconstitution
▶ Age as covariate on myeloid engraftment
PD scaling of myeloablation

Friberg model fits:

Mean transit time *versus* age

Dynamics slightly faster in smaller individuals, set point similar
PD scaling of myeloablation

- Poor engraftment significantly related with low AUC, death with high AUC:
- \( P(\text{successful engraftment}) \) versus age
PD scaling of CD4 reconstitution post HSCT

Data:
- 288 HSCT recipients with prospective validation in further 75

Biological prior:
- Normal lymphocyte and CD4 counts ↑ with ↓ age

This worries some:

Scaling question:
- How to incorporate age scaling \textit{a priori}?

CD4(t) = thymic out + proliferation − loss

\[
\frac{dX}{dt} = \lambda + pX - dX \quad (1)
\]

5 years, Monitoring by CD4 cell count in younger children is problematical because age is a highly influential variable. © 2006 Lippincott Williams & Wilkins

\textit{AIDS} 2006, \textbf{20}:1289–1294
Scaling proliferation and loss:

- Ki67 is a marker for proliferation found on CD4 T cells
- Bains 2009 found an exponential decline with age but why not size?

Allometric model \( y(wt) = 0.0127 \times \frac{(wt/70)^{-0.25}}{\log(wt) - 1.155} \), gives:

**Theoretical Article**

Some Scaling Principles for the Immune System

FREDERIK W WIEGEL\(^1\) and ALAN S PERELSON\(^2\)

Scaling aspects of lymphocyte trafficking

Alan S. Perelson\(^{a,*}\), Frederik W. Wiegel\(^b\)

\(^a\) Theoretical Division, Los Alamos National Laboratory, Los Alamos, NM 87545, USA
\(^b\) Institute of Theoretical Physics, University of Amsterdam, Valckenierstraat 65, 1018XG, Amsterdam, The Netherlands
Scaling thymic output:

- Thymus stops growing at 1 year, then epithelial space decreases by 70% by 20 years
- T cell receptor excision circles (TRECs) are a marker of cells released by thymus, progressively lost by division
- An expression for TREC changes with age derived by Bains et al 2009:

\[
\lambda(\tau) = \frac{y(\tau)N(\tau)\gamma}{\Delta(c - \gamma)},
\]  

where \(\lambda(\tau)\) is number of cells exported from the thymus per day for a person aged \(\tau\), \(\Delta, c\) and \(\gamma\) are constants, \(N(\tau)\) is the total number of CD4 cells for a person age \(\tau\), and \(y(\tau)\) is the proportion of cells expressing Ki67 at age \(\tau\).
PD scaling of CD4 reconstitution post HSCT

- Age (size) delineated for multivariable analysis:

- Extended to HIV (presented at WCoP 2016)

- Lymphocyte scaling used for CMV: I-17 [Ben Margetts] Modelling Cytomegalovirus Growth Kinetics in Immunocompromised Children
Pharmacodynamic scaling in children:

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PD scaling of meropenem in neonatal sepsis

Clinical response in antibiotic trials:
- Often no known source of infection, but resistance rates similar (Bielicki 2015)
- No standardisation of clinical endpoints

Biological prior:
- Neutrophil, macrophage and dendritic function impaired (Cuenca 2013)
- PKPD based on \textit{in vitro} MIC often used: $ft\times$MIC, AUC/MIC, $C_{\text{max}}$/MIC, changing PK profile shape may change most appropriate index (Nielsen 2011)
- Neonates need higher $ft\times$MIC based on \textit{in vitro} (Kristoffersson 2016)

Scaling question:
- Can we rely on \textit{in vitro} derived target?
PD scaling of meropenem in neonatal sepsis

Hypothesis:
▶ Attaining 61% $ft > MIC$ is sufficient for successful outcome

Data:
▶ NeoMero 1: Multi centre neonatal sepsis RCT (136 in meropenem arm)
▶ Optimally designed PK sampling (3 samples or single trough)
▶ 21 with a Gram negative blood stream infection with MIC
▶ Treatment failure defined as:
  ▶ modification of treatment
  ▶ death

Method:
▶ Investigate $ft > MIC$ versus outcome
Results:

▶ All had 61% $ft\geq MIC$, possible need for higher target (e.g. 100% $\geq 5\times MIC$ as per Li 2007 in adult LRTI)

▶ For another antimicrobial example see: III-52 [Frank Kloprogge]
Pharmacodynamics of vancomycin in children
Overview

Pharmacodynamic scaling in children:
- Introduction
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- Lessons from infectious diseases
- Conclusions
Lessons

- PK-only scaling may/may not be appropriate
- Biological priors useful for scaling (esp. adaptive immune system)
- Antimicrobial in vitro targets require further clinical evaluation/scaling

Final thought:
- PD scaling important, but (PK)PD only extrapolation still draws scepticism

- Appropriately scaled PKPD-guided small trial design (informing effect size, drug effect as parameter) maybe the future e.g. IDEAL, ASTERIX and INSPIRE consortia

Different treatment benefits were estimated by clinical trials performed in adults compared with those performed in children.

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London Pharmacometrics Interest Group
https://wiki.ucl.ac.uk/display/CM/London+Pharmacometrics+Interest+Group