



Towards Developing a Harmonising Framework for PK and/or PKPD Scaling for Pain Medications in the Paediatric Population

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Introduction

- Appropriate population pharmacokinetic (popPK) and pharmacokinetic-pharmacodynamic (PKPD) parameter scaling across the paediatric age range (birth to < 18 years of age) is necessary to account for the developmental changes in body size and organ maturation to determine the optimal drug dosing regimens tailored to each paediatric age group.
- In the therapeutic area of pain, extrapolation of adult to paediatric doses via exposure matching may be limited by age-related differences in pharmacodynamics (PD) and/or disease mechanisms, despite accounting for PK differences through exposure matching [1].

→ *Unmet need to harmonise PK and/or PKPD model parameter scaling for pain medications across the paediatric age range [2].*

Objectives

- Conduct a comprehensive literature review to identify previously published paediatric popPK and PKPD models in the therapeutic area of pain, specifically for paracetamol, morphine, and fentanyl, where individual-level data were available.
- Critically evaluate the identified models, with a particular focus on the parameter scaling approaches employed (e.g., body size, maturation functions), to inform best practices in paediatric dose optimisation.

Methods

- Protocol for literature search was developed with the following key inclusion criteria:
 - Study was in subjects < 18 years of age for any pain indication where paracetamol, morphine, or fentanyl were administered in at least one arm of study
 - Study reported popPK/PKPD modelling
 - Study contained individual-level data for either PK, efficacy, or PKPD endpoints
- Literature search was conducted in NCBI PubMed (see **Figure 1**)
- Relevant information was extracted and collated from the identified models

Results

- 25 published studies reporting popPK and/or PKPD models were identified and reviewed for paracetamol, morphine, and fentanyl.
- Most common pain indication: pre- or post-operative analgesia.
- Subjects' age across the studies spanned entire paediatric age range from neonates to adolescents (birth-17.9 years).
- Details of the parameter scaling in the identified popPK models are summarised in **Table 1**.
 - For 14 models with *fixed allometric exponents*: values fixed to 0.75 for clearance and 1 for volume of distribution.
 - For two models with *estimated allometric exponents*: estimated weight exponents on clearance were 1.1 and 1.4, and estimated weight exponent on volume of distribution was 0.8.
 - Example of rationale given for models with *no allometric scaling*: weight not significant on clearance or volume of distribution.
 - For models with *other parameter scaling*:
 - Allometric weight exponent on clearance was both fixed (to 0.75) and estimated (1.23). Fixing increased objective function value so exponent was estimated.
 - Weight-based exponential function best described metabolite formation/elimination.
 - Linear and power functions best described relationship between weight and clearance.

Table 1: Overview of Parameter Scaling in PopPK Models

Drug (N)	Median No. of Subjects (Range)	Models with Fixed Allo. Exp.	Models with Estimated Allo. Exp.	Models with No Allo. Exp.	Models with Other Para. Scaling
Paracetamol (8)	39 (9-144)	5	1	1	1
Morphine (12)	34 (15-875)	7	1	2	2
Fentanyl (5)	72 (14-164)	2	0	2	1
Total	NA	14	2	5	4

Allo.=allometric; Exp.=exponent; N=number of models; NA=not applicable; No.=number; Para.=parameter; PopPK=population pharmacokinetic.

Conclusions and Future Work

- Fixing allometric exponents was the most common parameter scaling approach in published paediatric popPK models in pain.
- Future work will compare the different maturation functions/exponents, and their relationship with parameters, reported in identified models to determine impact on clearance of pain medications.
- Additionally, future efforts will explore how PD parameters have been scaled across paediatric age groups.

Acknowledgements and References

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[1] Bardol M et al. Pharmacokinetic pharmacodynamic modeling of analgesics and sedatives in children. Paediatr Anaesth (2023); [2] Krekels EH et al. Systematic evaluation of the descriptive and predictive performance of paediatric morphine population models. Pharm Res (2011) 797-811



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