Consideration of PK/ PD studies

Oct 14th, 2021

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IQ Consortium

FDA-University of Maryland CERSI
Analgesic Clinical Trial Designs, Extrapolation, and Endpoints in Patients from Birth to Less Than Two Years of Age
Oct 13-14, 2021

MIDD – Model Informed Drug Development

Why MIDD useful in analgesic development for pediatric especially between birth to Less than 2yrs?

- Key Questions (KQ) -focus on why certain modeling is needed to answer clinical questions
- Data (utilize data from nonclinical to all phases in clinic from adult and older children)
- Data quality due to efficacy endpoints variations (pain perception and analgesic response)
- Assumptions setting, testing/evaluation to increase confident, especially on extrapolation and simulation study using existing PK, PD data based on assumption
- Modeling approach (tailor based on the KQ, data and assumptions)
- Accumulation of knowledge to ↑ prob. of success of new trial design to collect data or replace study
- Accelerate development with real-time quantitative assessment of emerging data
- Utilize data from similar class of MoA in various pediatric population
- Impact: Support dose finding and selection based on TI
- Support communication for sponsors and regulators decision making

Making use of data from existing PK/PD studies

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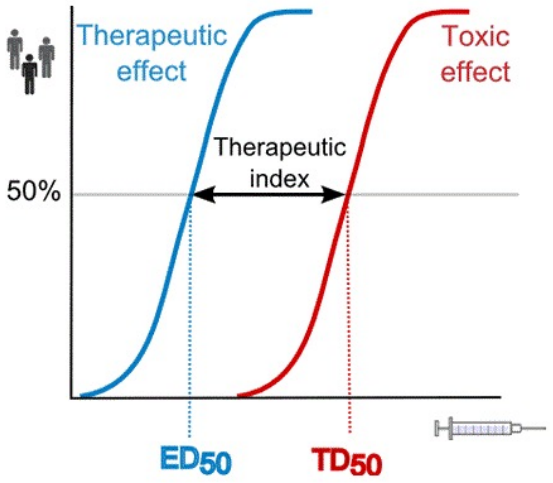
Optimize future PK/PD studies (collect useful data)

↓

Robust model based on data PK/PD studies

↓

Extrapolate to efficacy



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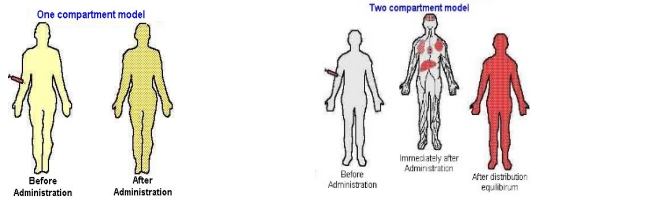
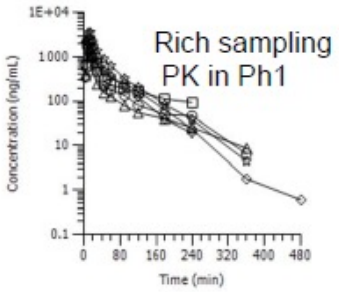
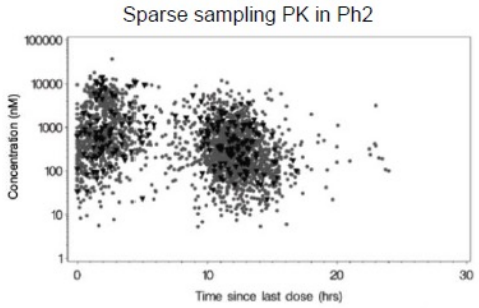
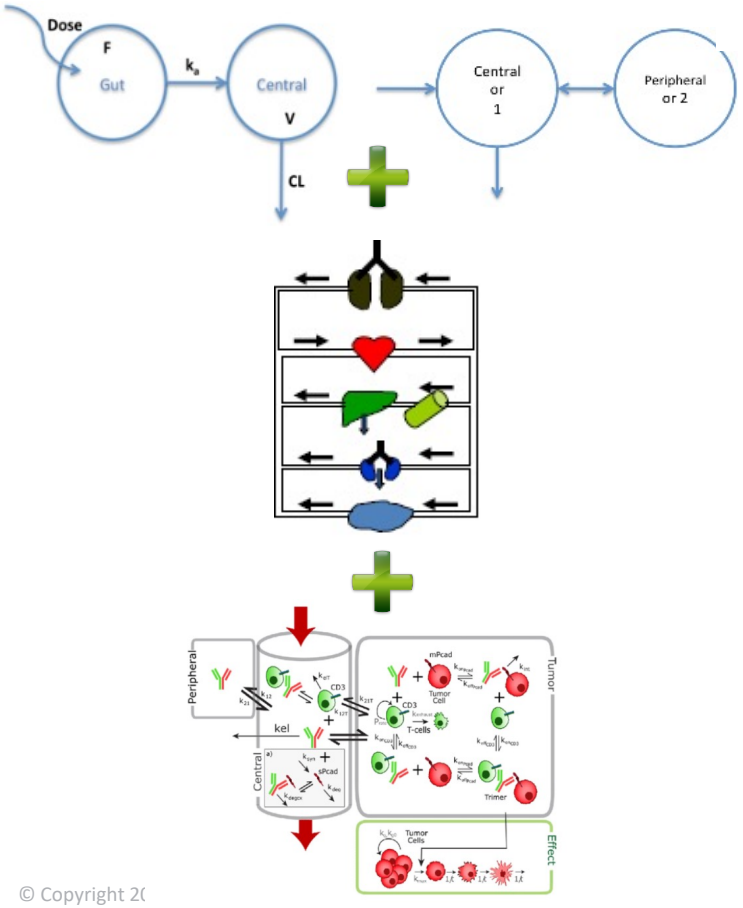
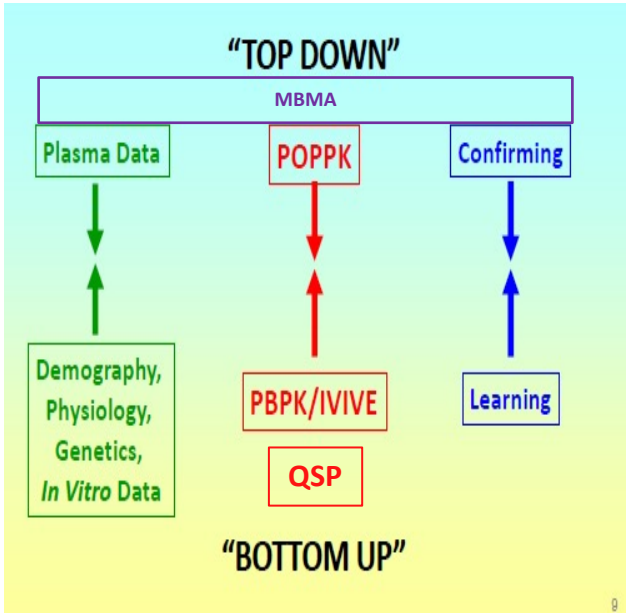
Empirical Approach vs. Mechanistic Approach for Simulation and Extrapolation?

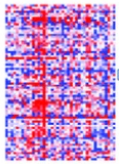












Consideration:

- Objective/ Key questions?
- Robustness of prior knowledge e.g. animal models, adult models etc.
- Assumption setting and evaluation!
- Amount and quality of data (sample and size)
- Describe? Extrapolation? Extend?
- Clinical trial simulation?

Usage: FTIH, pediatric, DDI and Renal and Hepatic impairment (where appropriate), formulation development

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PK-PD data, modeling in acute and chronic pain

EXPERT REVIEWS

Pharmacokinetic–pharmacodynamic modeling in acute and chronic pain: an overview of the recent literature

Expert Rev. Clin. Pharmacol. 4(6), 719–728 (2011)

Christian Martini[1], Erik Olofsen[2], Ashraf Yassen[2], Leon Aarts[1] and Albert Dahan[*1]

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[2]Global Clinical Pharmacology and Exploratory Development, Astellas Pharma Global Development Europe, Leiderdorp, The Netherlands
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In acute and chronic pain, the objective of pharmacokinetic–pharmacodynamic (PKPD) modeling is the development and application of mathematical models to describe and/or predict the time course of the pharmacokinetics (PK) and pharmacodynamics (PD) of analgesic agents and link PK to PD. Performing population PKPD modeling using nonlinear mixed effects modeling allows, apart from the estimation of fixed effects (the PK and PD model estimates), the quantification of random effects as within- and between-subject variability. Effect-compartment models and mechanism-based biophase distribution models that incorporate drug-association and -dissociation kinetics are applied in PKPD modeling of pain treatment. Mechanism-based models enable the quantification of the rate-limiting factors in drug effect owing to drug distribution versus receptor kinetics (since receptor kinetics are nonlinear they are discernable from the linear effect-compartment kinetics). It is a helpful technique in understanding the complex behavior of specific analgesics, such as buprenorphine, but also morphine and its active metabolite morphine-6-glucuronide, especially with respect to the reversal of opioid-induced side effects, most importantly life-threatening respiratory depression. One approach in chronic pain studies is the application of mixture models. Mixture models do not necessarily need to take PK data into account and allow the objective differentiation of measured responses to analgesics into

in analyzing Phase I and
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rstanding the interaction
play an important role in
orementioned techniques
ugs in acute and chronic

ent • epidural analgesia
kinetics • PKPD modeling

Table 1. Population pharmacodynamic model estimates for various analgesic agents and naloxone using pain relief or respiration as the effect parameter: studies performed in healthy volunteers or patients.

Drug	$t_{1/2}k_{e0}$	k_{e0} (ml/ng/min)	K_{out} (min^{-1})	K_d (k_{off}/k_{on})	C_{50}	Effect parameter	Population	Ref.
Morphine (men)	1.6 h				250 nM	Antinociception	V	[13]
Morphine (women)	4.8 h				125 nM	Antinociception	V	[13]
Morphine-6-glucuronide	6–8 h				750 nM	Antinociception	V	[12,14]
Morphine	1.2 h	0.85	0.14	160 nM		Respiration	V	[17]
Morphine-6-glucuronide	2.7 h	0.04	0.03	880 nM		Respiration	V	[17]
Naloxone	5–8 min				0.5–2 nM	Respiration	V	[17]
Morphine	1.7 h				124 nM	Postoperative analgesia	P	[20]
Morphine-6-glucuronide	3 h				13 nM	Postoperative analgesia	P	[20]
Buprenorphine	75 min	0.25	0.01	0.09 nM		Respiration	V	[6]
Fentanyl	16.4 min	>100	>100		1140 ng/ml	Respiration	V	[6]
Buprenorphine	155 min	0.06	0.08	2.66 nM		Antinociception	V	[24]
S-ketamine	[1]				373–2200 ng/ml[1]	Antinociception	V	[28]
S-ketamine	11 days[1]				10.5 ng/ml	Chronic CRPS pain relief	P	[34]
Pregabalin	11 h				1.54 µg/ml	Chronic fibromyalgia pain relief	P	[35]
SC-75416					5500 ng/ml	Postoral surgery pain relief	P	[29]
Rofecoxib					284 ng/ml	Postoral surgery pain relief	P	[29]
Valdecoxib					68 ng/ml	Postoral surgery pain relief	P	[29]
Ibuprofen					6840 ng/ml	Postoral surgery pain relief	P	[29]
Ibuprofen	28 min				10,200 ng/ml	Postoral surgery pain relief	P	[30]
Acetaminophen	53 min				10 mg/l	Post-tonsillectomy pain relief	P	[32]

[1]$t_{1/2}k_{e0}$ is calculated as $\ln 2/k_{e0}$.
[2]No hysteresis observed between plasma concentration and effect.
[3]C_{50} varied depending on the nociceptive assay employed (see text).
[4]The value of 11 days represent a rate-constant form disease modulation ($t_{1/2}k$) unrelated to the blood effect-site equilibration $t_{1/2}k_{e0}$.
C_{50}: Steady-state concentration causing 50% of the effect; CRPS: Complex regional pain syndrome; K_d: Equilibrium dissociation constant; k_{e0}: Effect-site equilibration constant; K_{out}: Receptor dissociation constant; K_{on}: Receptor-association constant; P: Patients; $t_{1/2}$: Half-life; V: Volunteers.

REVIEW

Pain assessment using the Adolescent Pediatric Pain Tool: A systematic review

Ananda Maria Fernandes PhD[1], Catarina De Campos BSN[1], Luis Batalha PhD[1], Ana Perdigão MSc[1], Eufemia Jacob PhD[2]

A Fernandes, C De Campos, L Batalha, A Perdigão, E Jacob. Pain assessment using the Adolescent Pediatric Pain Tool: A systematic review. Pain Res Manag 2014;19(4):212-218.

BACKGROUND: The Adolescent Pediatric Pain Tool (APPT) is a multidimensional pain assessment tool designed to assess pain location (body outline diagram), intensity (word graphic rating scale) and quality (list of pain descriptors) in hospitalized children eight to 17 years of age.
OBJECTIVES: To identify the age range, health conditions, settings and purpose for which APPT has been used; the components of the APPT that have been used; and the reported clinical and research utility of the APPT.
METHODS: A systematic review of published studies using the APPT was performed. Studies were identified through electronic searches in CINAHL, Medline, PubMed, SciELO and PsycInfo.
RESULTS: Twenty-three studies were analyzed. APPT has been used in patients between two and 68 years of age, with various acute and chronic

L'évaluation de la douleur à l'aide de l'outil d'évaluation pédiatrique de la douleur à l'adolescence : une analyse systématique

HISTORIQUE : L'outil APPT d'évaluation pédiatrique de la douleur à l'adolescence est un outil multidimensionnel conçu pour évaluer le foyer (schéma du corps humain), l'intensité (échelle d'évaluation graphique en mots) et la qualité (liste de descripteurs de la douleur) de la douleur chez les enfants hospitalisés de huit à 17 ans.
OBJECTIFS : Déterminer les tranches d'âge, les maladies, les milieux et les raisons pour lesquels l'outil APPT a été utilisé, les volets de l'outil APPT qui ont été utilisés et l'utilité de l'outil APPT en clinique et en recherche.
MÉTHODOLOGIE : Les chercheurs ont mené une analyse systématique des études publiées faisant appel à l'outil APPT. Ils ont colligé les études au moyen de recherches électroniques dans CINAHL, Medline, PubMed,

TABLE 2
Components of the Adolescent Pediatric Pain Tool, outcome variables and number of studies

Component	Studies, n	Outcome variables	Studies, n
Body outline diagram	19	Total number of sites	13
		Location of most frequently marked site	4
		Surface area	2
Word graphic rating scale	21	Mean pain intensity	12
		Pain in 3 categories: low, high, worst pain	1
		Pain in 4 categories: no pain (0), mild (1–3), moderate (4–6) and severe (7–10)	1
		Pain in 5 categories: 0 (no pain) to 4 (most pain ever)	2
		Not reported	5
Pain quality descriptors	19	Mean number of words selected	13
		Mean number of words selected in sensory, affective, evaluative, temporal dimensions	8
		Percentage of words selected	1
		Percentage of words selected in sensory, affective, evaluative, temporal dimensions	2
		Number of participants reporting ≥1 word in sensory, affective, evaluative, temporal dimensions	1
		Not reported	1

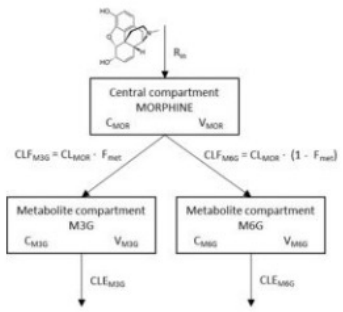
Table 1: Pain Scale, Population Tested and Validity

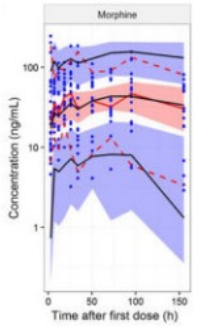
Pain Scale	Population Tested and Dimensions	Validity/Reliability
The CRIES	• pilot study of 20 neonates postoperatively • Posture/tone, sleep pattern, expression, color, cry, respirations, heart rate, saturations, blood pressure, nurse's perception	• Discriminant validity (limited reporting of statistics but trend toward differences in pain that would be expected between infusion started with or without bolus dose) • Content validity (scores reflecting nurses' perceptions of pain).
The Neonatal Infant Pain Scale (NIPS)	• 38 preterm and term infants and 90 procedures observed • Facial expression, cry, breathing patterns, arm movement, leg movement, and state of arousal	• Interrater reliability (Pearson's correlations 0.92 to 0.97) • Internal consistency (Cronbach's alphas 0.87 to 0.95) • Content validity (survey) • Concurrent validity (correlations 0.53 to 0.84 when compared with visual analogue scale) • Construct validity (change in pain scores over time was seen with main effect of time being statistically significant, $F = 18.97$, $P < 0.001$)
The Premature Infant Pain Profile (PIPP)	• 4 data sets (n = 27, 39, 48, & 124) of infants ranging in gestation from 28 to 40 weeks • Gestational age, behavioral state, heart rate, oxygen saturation, brow bulge, eye squeeze, and nasolabial furrow.	• Internal consistency (correlation coefficients for individual items 0.59 to 0.76; the standardized item alpha for 6 of the items was 0.71) • Content validity (experts and literature) • Construct validity (scores between no pain and pain situations, paired *t*-test = 12.24, two-tailed $P < 0.0001$)

Pharmacokinetic Models of Morphine and its Metabolites in Neonates:

Systematic Comparisons of Models from the Literature, and Development of a New Meta-Model

Katrine Rørbæk Knøsgaard, M.Sc.[1], David John Richard Foster, Ph.D.[2], Mads Kreilgaard, Ph.D.[1], Eva Sverrisdóttir, Ph.D.[1], Richard Neil Upton, Ph.D.[2,*], and Johannes N. van den Anker, MD, Ph.D.[3,4,5]





Population Pharmacokinetics of Intravenous Paracetamol (Acetaminophen) in Preterm and Term Neonates: Model Development and External Evaluation

Sarah F. Cook[1], Jessica K. Roberts[2], Samira Samiee-Zafarghandy[3,4], Chris Stockmann[2,5], Amber D. King[1], Nina Deutsch[6], Elaine F. Williams[3], Karel Allegaert[7,8], Diana G. Wilkins[1,9], Catherine M. T. Sherwin[2], and John N. van den Anker[3,10,11,12]

Study information for the model-building and external evaluation datasets

	Study 1, model-building dataset	Study 2, external dataset (PARANEO) [6]
NCT identifier	01328808	00969176
Study description	Phase II/III, multiple-dose study of intravenous paracetamol	Phase II/III, multiple-dose study of intravenous paracetamol
Study drug	Ofirmev (10 mg/mL)	Paracetamol Sintetica (10 mg/mL)
Sampling route	Arterial	Arterial
Analytical method	HPLC–MS/MS	HPLC–UV
Subjects	35 neonates	60 neonates
Samples (*n*)	260	430
Age subject [median (range)]	8 (3–11)	7 (2–11)
Primary indication for intravenous paracetamol [*n* (%)]		
Postoperative analgesia	19 (54)	33 (55)
Cardiac surgery	19 (54)	15 (25)
Thoracic surgery	0 (0)	11 (18)
Abdominal surgery	0 (0)	6 (10)
Other	0 (0)	1 (2)
Medical conditions	16 (46)	27 (45)
Alprostadil administration	0 (0)	8 (13)
Procedural/respiratory	16 (46)	8 (13)
Traumatic pain	0 (0)	5 (8)
Fever	0 (0)	3 (5)
Other	0 (0)	3 (5)
Gestational status [*n* (%)]		
Extreme preterm (<28 weeks' GA)	10 (29)	5 (8)
Preterm (<37 weeks' GA)	17 (49)	28 (47)
Full-term (37–42 weeks' GA)	18 (51)	32 (53)
Current body weight[a] (kg) by gestational age subgroup [median (range)]		
Extreme preterm (<28 weeks' GA)	0.69 (0.55–1.30)	0.90 (0.61–1.41)
Preterm (<37 weeks' GA)	0.96 (0.46–2.30)	2.08 (0.61–3.44)
Full-term (37–42 weeks' GA)	3.16 (2.70–4.20)	3.22 (1.80–4.30)
Postnatal age[a] (days) by gestational age subgroup [median (range)]		
Extreme preterm (<28 weeks' GA)	10 (1–26)	17 (6–24)
Preterm (<37 weeks' GA)	9 (1–26)	6 (1–27)
Full-term (37–42 weeks' GA)	6 (2–12)	2 (1–10)

GA gestational age, *HPLC* high-performance liquid chromatography, *MS/MS* tandem mass spectrometry, *NCT* National Clinical Trial, *PARA-NEO* Paracetamol in Neonates, *UV* ultraviolet detection
[a]On the day of the first paracetamol dose

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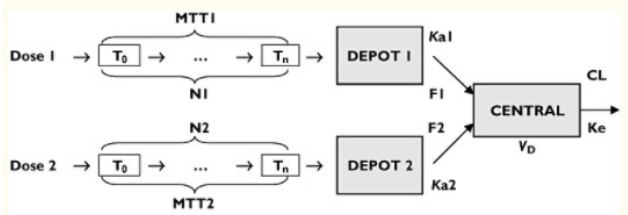
Challenge of mathematic model development

- Even we have data, there are challenges of the complexity of the mathematical model e.g. diclofenac, if we don't consider the use of PBPK but with simpler compartmental model/s

- A non-steroidal anti-inflammatory drug (NSAID)
- Reduce pain and inflammatory
- Sodium salt
- Linear PK in adult (25mg - 100mg)
- Commonly used "off label" for acute pain in children (0.5-2.5mg/kg)
- License for pediatric oral formulation is not available
- PK model: new oral dose, 1mg/kg in pediatric patient
- (aged 1-12)
- Adult rich data (30 healthy volunteers) - 50mg
- 70 pediatric patients – minor surgery – pre-op dose
- Similar AUC
- Pediatric patient won't higher dose

	Frequency given as mean (range) or number (percentage) as appropriate		
	Children $n = 70$	Adults $n = 30$	Pooled $n = 100$
Age (years)	3 (1–12)	21 (18–28)	9 (1–28)
Weight (kg)	17 (9–37)	72 (48–94)	34 (9–94)
Height (cm)	101 (69–146)	170 (158–187)	122 (69–187)
Male	41 (59%)	14 (47%)	55 (55%)
Female	29 (41%)	16 (53%)	45 (45%)
Surgery type:			
Dermatology	54 (77%)	–	–
General*	12 (17%)	–	–
Plastic*	4 (6%)	–	–



Tn = Transit compartment.

The following fixed effects were estimated in NONMEM:

MTT1 = Mean transit time into first depot compartment (h).
N1 = Number of transit compartments prior to first depot compartment.
F1 = Fraction absorbed from first depot compartment.
$t_{1/2A1}$ = Absorption half-life from first depot compartment (h) = ln2/Ka1.
MTT2 = Mean transit time into second depot compartment (h).
N2 = Number of transit compartments prior to second depot compartment.
F2 = Fraction absorbed from second depot compartment (fixed to = 1 – F1).
$t_{1/2A2}$ = Absorption half-life from second depot compartment (h) = ln2/Ka2.
V_D = Volume of distribution (l).
CL = Clearance ($l\,h^{-1}$) = V_D x Ke.

Venot, A. et al, J. Pharmacokinet. Biopharm. Vol. 15, No. 2, 179-189, 1987
Standing, J. F. et al, BJCP 2008
Cheung, Standing, Aarons, presentation 2008 PAGE

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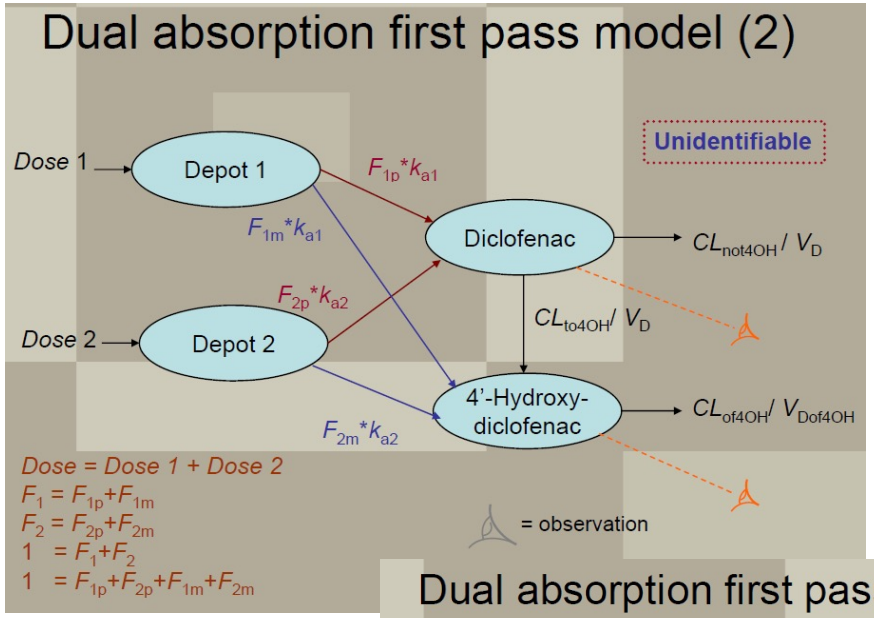
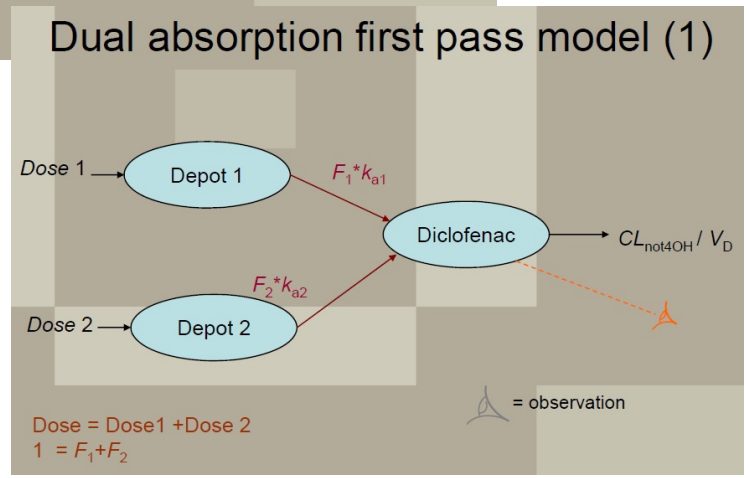
Diclofenac dual absorption first pass model

Mathematical structural identifiability





- Proven that the delay mechanism occurring prior to the introduction of the absorption in the 2nd depot compartment in the model enhances the identifiability status of the model
- From an unidentifiable model to a globally identifiable model = which essential to predict unique and stable PK parameter and model to link with PD/efficacy

- A major metabolite 4'-hydroxydiclofenac
- (CYP2C9)
- CL_{to4OH}, a useful *in vivo* marker of CYP2C9
- expression
- Previous *in vitro*: CYP2C9 expression to be adult
- equivalent by age five months
- CYP2C9 ontogeny using the base model

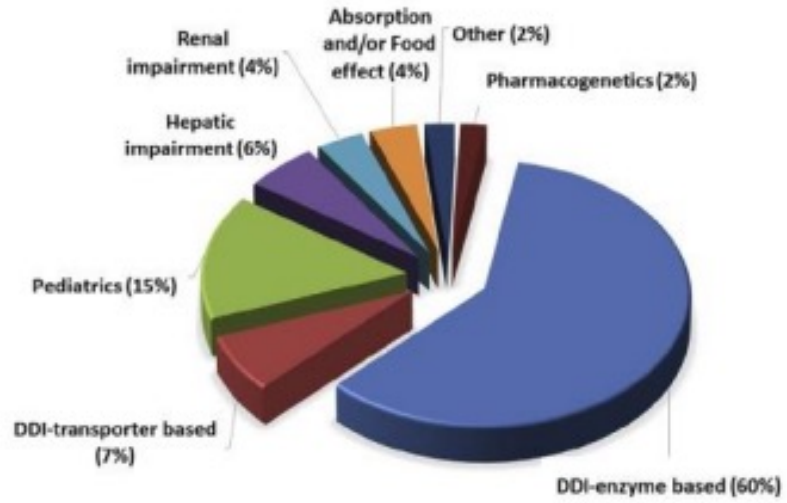
Cheung, Standing, Aarons, presentation 2008 PAGE

PBPK model applications in drug development Increased regulatory acceptance over the years

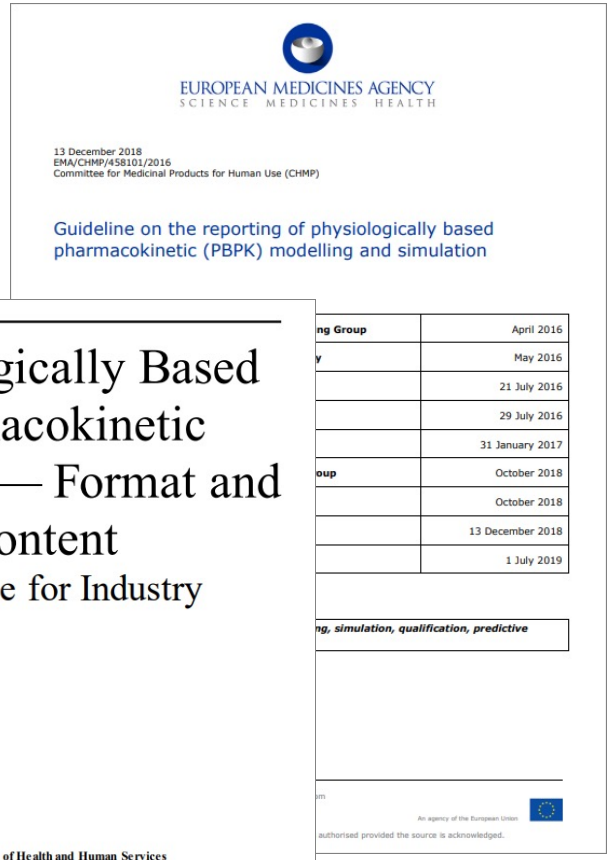
Number of NDA Submissions Per Year Containing PBPK Analyses and Respective Areas of Application, in the Period of 2008 to 2017

Area of Application	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total
Total Submissions	1	3	1	5	5	11	13	11	17	27	94
DDI total	1	3	0	3	3	7	9	5	15	26	72
DDI-enzyme based	1	3	0	2	3	5	9	5	12	11	52
DDI-P-gp transporter	0	0	0	1	0	1	0	0	1	9	12
DDI-transporter based	0	0	0	0	0	1	0	0	2	6	8
Specific populations											
Pediatrics	0	0	0	2	1	2	1	1	2	3	12
Hepatic impairment	0	0	1	0	0	1	2	1	1	2	8
Renal impairment	0	0	0	0	0	0	0	1	2	1	4
Oral absorption	0	0	0	0	1	3	1	2	1	0	8
Biologics	0	0	0	0	0	0	1	0	0	1	2
Others	0	0	0	0	0	1	0	1	1	1	4
Total intended applications[a]	–	–	–	–	–	–	–	–	–	–	110

[a] The total number of intended PBPK applications exceeds the number of NDA submissions containing PBPK analyses as each submission might contain more than 1 area of application.



The focus should be to PD, but PK and exposure still essential for extrapolation and linking to PD especially < 2yr

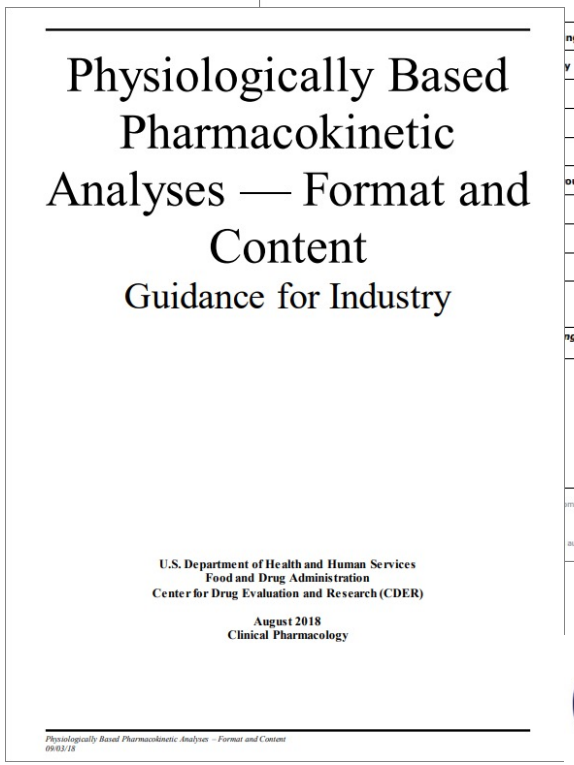

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2018
EMA/CHMP/458101/2016
Committee for Medicinal Products for Human Use (CHMP)

Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation

ng Group	April 2016
y	May 2016
	21 July 2016
	29 July 2016
	31 January 2017
oup	October 2018
	October 2018
	13 December 2018
	1 July 2019

ng, simulation, qualification, predictive


Physiologically Based Pharmacokinetic Analyses — Format and Content

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

August 2018
Clinical Pharmacology

Physiologically Based Pharmacokinetic Analyses – Format and Content
09/03/18

Grimstein et al. J Pharm Sci 2019

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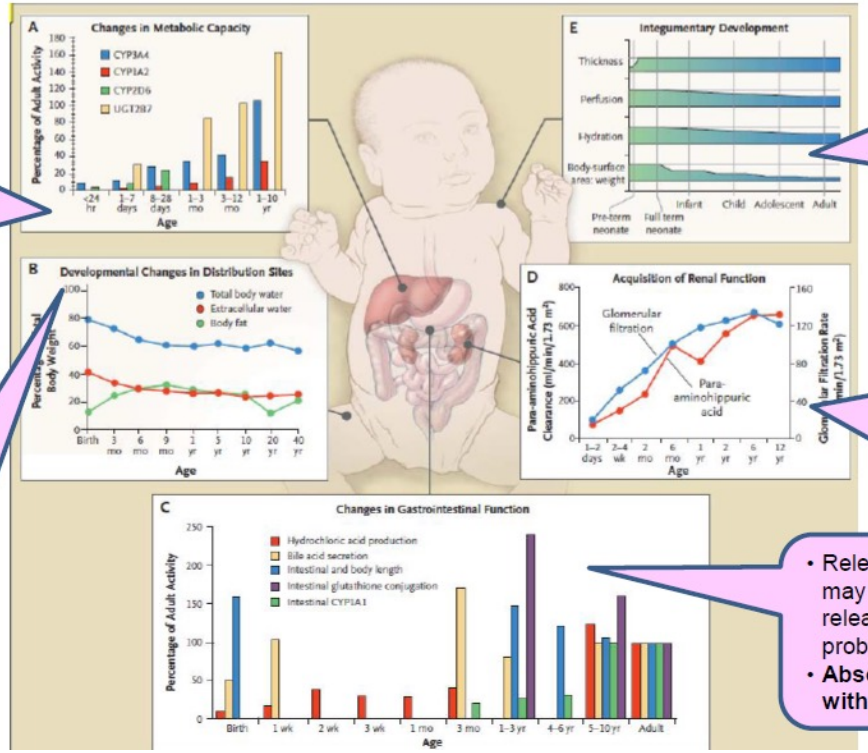
Maturation impact to PK

Overview of Developmental Changes of ADME

Determining appropriate dosing regimes is complex owing to the physiological and anatomical changes that occur during childhood

- **Drug-metabolising enzymes show age-dependent changes** in activity
- **Time of maturation** is enzyme-specific



Higher percutaneous absorption; higher BSA/WT and thus mg/kg dose

Renal excretion is reduced in neonates due to immature GFR, tubular secretion and reabsorption
GFR approx. 90% of adult value at age of 1 year

Body composition depends on age – so does drug distribution: Low plasma protein concentrations and a higher body water composition
Absorption can be affected by differences in gastric pH and stomach emptying time

- Release from **formulation** may be modified (extended release and enteric coating problematic)
- **Absorption will change with age**

Clinical Pharmacology & Therapeutics

Article

Predictive Performance of Physiologically Based Pharmacokinetic (PBPK) Modeling of Drugs Extensively Metabolized by Major Cytochrome P450s in Children

Wangda Zhou, Trevor N. Johnson, Khanh H. Bui, S.Y. Amy Cheung, Jianguo Li, Hongmei Xu, Nidal Al-Huniti, Diansong Zhou

First published: 13 October 2017 | https://doi.org/10.1002/cpt.905 | Citations: 25

CPT: Pharmacometrics & Systems Pharmacology

Original Article | Open Access

Predictive Performance of Physiologically Based Pharmacokinetic and Population Pharmacokinetic Modeling of Renally Cleared Drugs in Children

W Zhou, TN Johnson, H Xu, SYA Cheung, KH Bui, J Li, N Al-Huniti, D Zhou

First published: 27 August 2016 | https://doi.org/10.1002/psp4.12101 | Citations: 43

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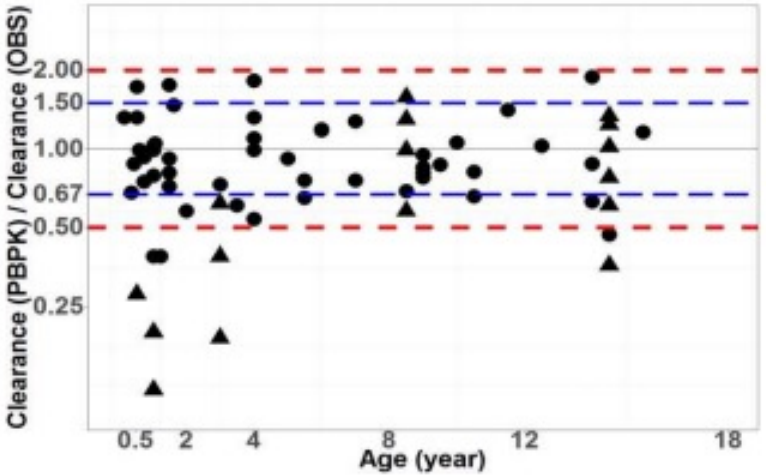
Predictive Performance of PBPK Modeling of Drugs

- PBPK modeling is a useful tool for extrapolation of PK profiles in children with only adult clinical trial results and is exceptionally valuable to guide selection of doses in first-in-pediatric studies
- A total of 67 clinical studies from 10 CYP metabolized drugs were available across all pediatric age groups (1 month to <18 years)
- Predictive performance of PBPK modeling approach was evaluated using 10 drugs extensively metabolized by major CYP enzymes, desloratadine, diclofenac, itraconazole,, lansoprazole, montelukast, ondansetron, sufentanil, theophylline and tramadol

PBPK models can reasonably predict exposure in children 1 month and older for an array of predominantly CYP metabolized drugs. The default ontogeny functions within Simcyp should be applied for all CYP enzymes except for CYP2C8, where the function proposed by Upreti and Wahlstrom should be used

Opioid
NSAID



Clinical Pharmacology & Therapeutics

Article

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OVERALL PREDICTIVITY of PBPK MODELS: Filled circles represent mean ratios of PBPK predicted clearance over observed clearance of all drugs (except esomeprazole, presented as filled triangles) in children 1 month to 18 years old. Blue dashed lines and red dotted lines represent the 1.5-fold and 2-fold error.

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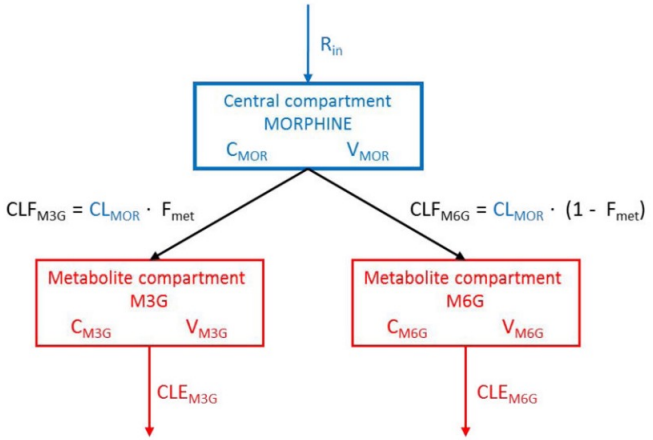
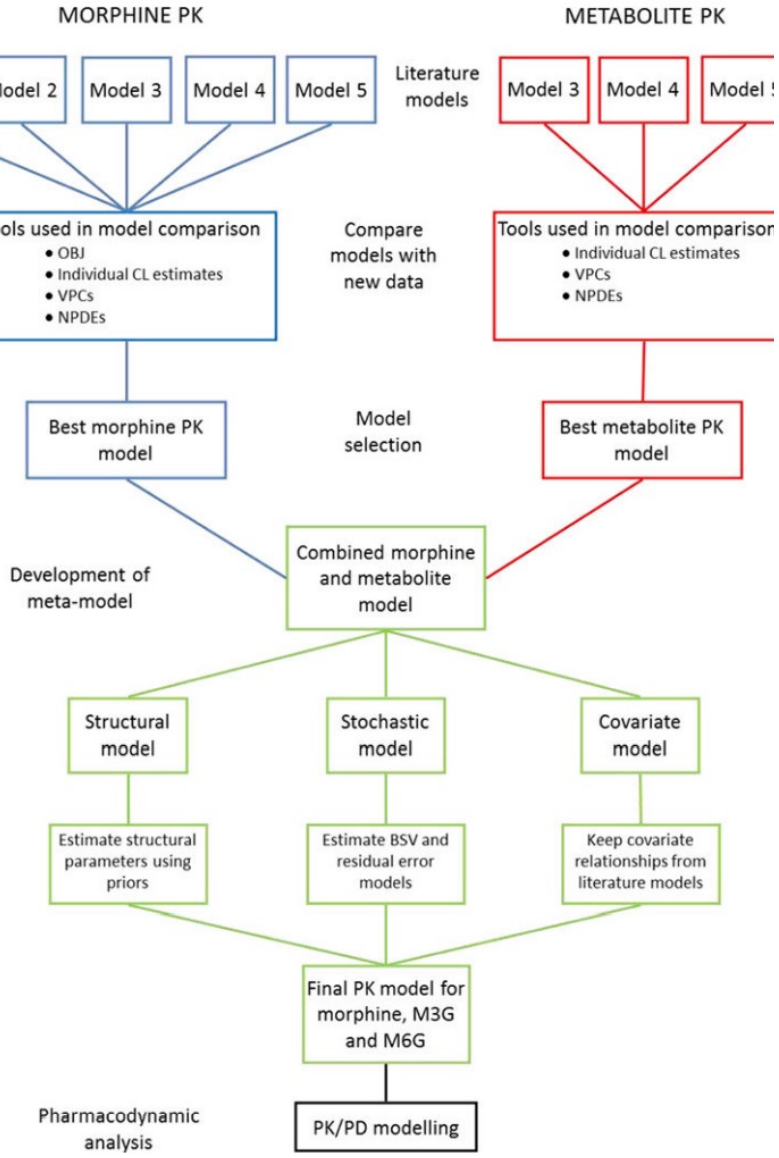
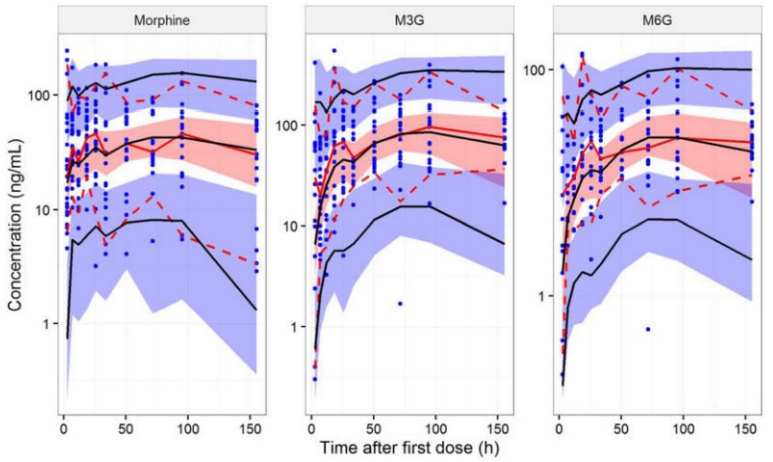
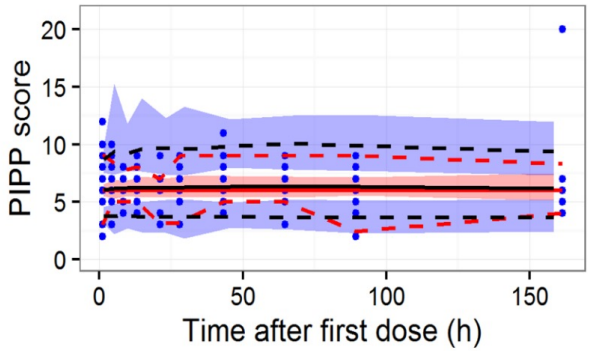
Example Morphine neonatal PKPD model (prior and meta-model)



Model	Population	Site of blood sampling	Structural model	Metabolites	Covariates
Model 1 Anand et al. 2008	184 term neonates to children, with PNA of 195 (0–1070) days, and a bodyweight of 5.9 (1.9–16.8 kg) 446 preterm neonates with PNA of 2 (0–20) days, PMA of 27.4 (23–32) weeks and bodyweight of 1.04 (0.42–2.44) kg	Arterial	1-compartment model	none	Power equation for weight with fixed exponent of 0.75 Sigmoidal equation for maturation (PMA) Scale factor for clearance and volume in preterm neonates
Model 2 Wang et al. 2013	475 subjects (neonates, young children, older children and adults, with PNA 0.1 days-36 years and bodyweight of 0.56–85 kg	Arterial	2-compartment model	none	Power equation for weight with a bodyweight dependent exponent
Model 3 Wang et al. 2013	338 neonates to children, with PNA of 0–1070 days and bodyweight of 0.57–16.8 kg 20 healthy adults, aged 20–37 years, with a bodyweight of 56–85 kg	Arterial	2-compartment model for morphine and 1 compartment for the metabolite	M3G	Power equation for weight with a bodyweight dependent exponent
Model 4 Bouwmeester et al. 2004	184 term neonates to children, with a PMA of 195 (0–1070) days, and a bodyweight of 5.9 (1.9–16.8) kg	Arterial	1-compartment model for morphine, and 1 compartment for each of the metabolites	M3G, M6G	Power equation for weight with fixed exponent of 0.75 Exponential equation for maturation (PNA)
Model 5 Knibbe et al. 2009	248 neonates to children, with a PNA of 33 (0.95–203) days, PMA of 41.9 (35.6–62.6) weeks and a bodyweight of 3.58 (2.2–7.0) kg	Arterial	2-compartment model for morphine, and 1 compartment for each of the metabolites	M3G, M6G	Power equation for weight with an estimated exponent of 1.44 Scale factor for clearance in neonates <10 days PNA







Example Acetaminophen (Paracetamol) Model in preterm, neonates and infants

Population Pharmacokinetics of Intravenous Paracetamol (Acetaminophen) in Preterm and Term Neonates: Model Development and External Evaluation

Sarah F. Cook[1], Jessica K. Roberts[2], Samira Samiee-Zafarghandy[3,4], Chris Stockmann[2,5], Amber D. King[1], Nina Deutsch[6], Elaine F. Williams[3], Karel Allegaert[7,8], Diana G. Wilkins[1,9], Catherine M. T. Sherwin[2], and John N. van den Anker[3,10,11,12]

Study information for the model-building and external evaluation datasets

	Study 1, model-building dataset	Study 2, external dataset (PARANEO) [6]
NCT identifier	01328808	00969176
Study description	Phase II/III, multiple-dose study of intravenous paracetamol	Phase II/III, multiple-dose study of intravenous paracetamol
Study drug	Ofirmev (10 mg/mL)	Paracetamol Sintetica (10 mg/mL)
Sampling route	Arterial	Arterial
Analytical method	HPLC–MS/MS	HPLC–UV
Subjects	35 neonates	60 neonates
Samples (*n*)	260	436
N per subject [median (range)]	8 (3–11)	7 (2–11)
Primary indication for intravenous paracetamol [*n* (%)]		
Postoperative analgesia	19 (54)	33 (55)
Cardiac surgery	19 (54)	15 (25)
Thoracic surgery	0 (0)	11 (18)
Abdominal surgery	0 (0)	6 (10)
Other	0 (0)	1 (2)
Medical conditions	16 (46)	27 (45)
Alprostadil administration	0 (0)	8 (13)
Procedural/respiratory	16 (46)	8 (13)
Traumatic pain	0 (0)	5 (8)
Fever	0 (0)	3 (5)
Other	0 (0)	3 (5)
Gestational status [*n* (%)]		
Extreme preterm (<28 weeks' GA)	10 (29)	5 (8)
Preterm (<37 weeks' GA)	17 (49)	28 (47)
Full-term (37–42 weeks' GA)	18 (51)	32 (53)
Current body weight[a] (kg) by gestational age subgroup [median (range)]		
Extreme preterm (<28 weeks' GA)	0.69 (0.55–1.30)	0.90 (0.61–1.41)
Preterm (<37 weeks' GA)	0.96 (0.46–2.80)	2.08 (0.61–3.66)
Full-term (37–42 weeks' GA)	3.16 (2.70–4.20)	3.22 (1.80–4.30)
Postnatal age[a] (days) by gestational age subgroup [median (range)]		
Extreme preterm (<28 weeks' GA)	10 (1–26)	17 (6–24)
Preterm (<37 weeks' GA)	9 (1–26)	6 (1–27)
Full-term (37–42 weeks' GA)	6 (2–12)	2 (1–10)

GA gestational age, *HPLC* high-performance liquid chromatography, *MS/MS* tandem mass spectrometry, *NCT* National Clinical Trial, *PARANEO* Paracetamol in Neonates, *UV* ultraviolet detection

[a]On the day of the first paracetamol dose

Randomized Population Pharmacokinetic Analysis and Safety of Intravenous Acetaminophen for Acute Postoperative Pain in Neonates and Infants

The Journal of Clinical Pharmacology
2020, 60(1) 16–27

DOI: 10.1002/jcph.1508

Gregory B. Hammer, MD[1], Lynne G. Maxwell, MD[2], Brad M. Taicher, DO, MBA[3], Mihaela Visoiu, MD[4], David S. Cooper, MD, MPH[5], Peter Szmuk, MD[6], Leng Hong Pheng, PhD[7], Nathalie H. Gosselin, PhD[7], Jia Lu, PhD[8], and Krishna Devarakonda, PhD, FCP[8]

	Intravenous Acetaminophen Groups			Control Groups			
	Group A	Group B	Group A+B	Group C	Group D	Group C+D	Total
Number of subjects randomized, total	66	72	138	35	42	77	215
Neonates	15	13	28	9	8	17	45
Younger infant	17	23	40	8	10	18	58
Intermediate-age infants	19	18	37	12	10	22	59
Older infants	15	18	33	6	14	20	53
Number of subjects completed, total (%)	52 (78.8)	55 (76.4)	107 (77.5)	26 (74.3)	26 (61.9)	52 (67.5)	159 (74.0)
Neonates	13 (86.7)	12 (92.3)	25 (89.3)	7 (77.8)	6 (75.0)	13 (76.5)	38 (84.4)
Younger infants	14 (82.4)	15 (65.2)	29 (72.5)	7 (87.5)	7 (70.0)	14 (77.8)	43 (74.1)
Intermediate-age infants	13 (68.4)	14 (77.8)	27 (73.0)	6 (50.0)	3 (30.0)	13 (59.1)	40 (67.8)
Older infants	12 (80.0)	14 (77.8)	26 (78.8)	6 (100.0)	6 (42.9)	12 (60.0)	38 (71.7)

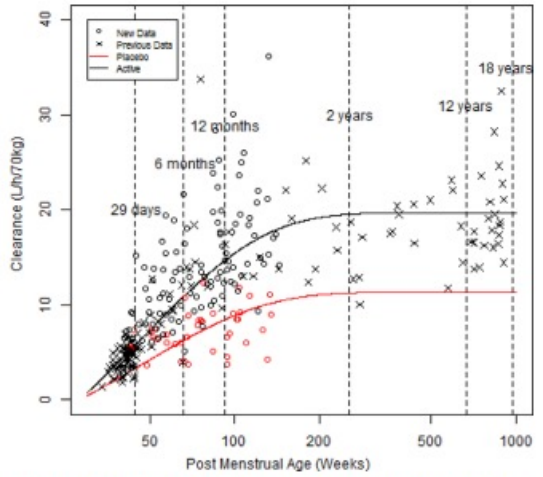


Figure 4. The relationship between clearance and postmenstrual age: a sigmoidal pattern with a clearance plateau of 18.9 L/h per 70 kg observed in neonates, infants, children, and adolescents.

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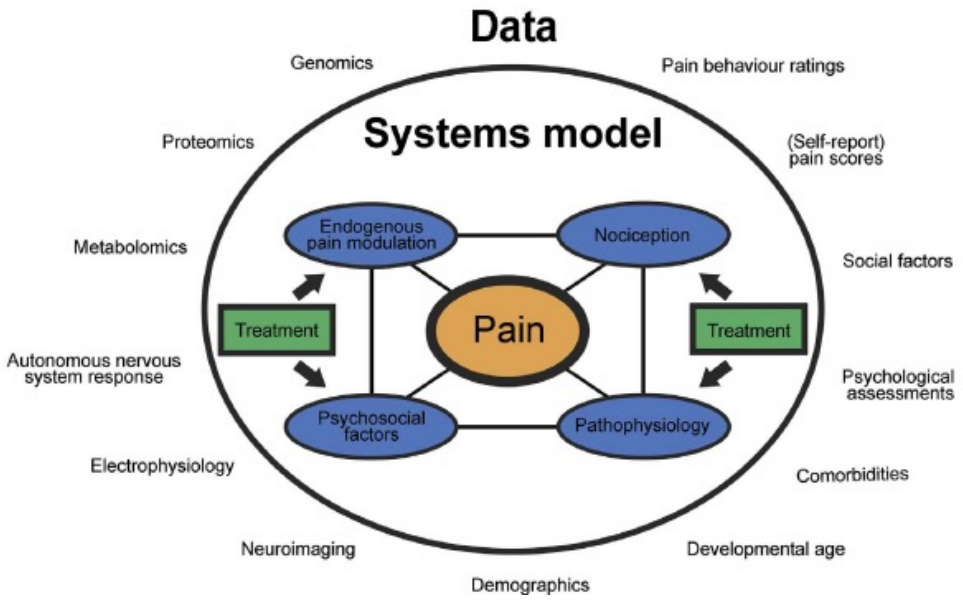
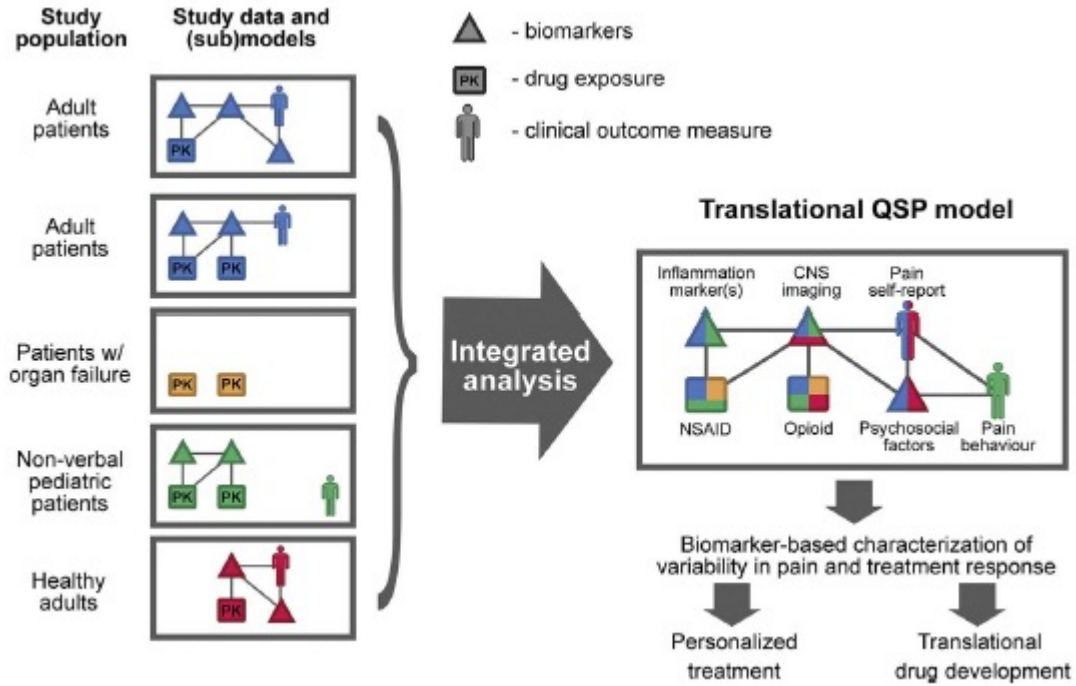
Quantitative System Pharmacology



- Systems view of the complexity and connectivity of clinical pain. A systems understanding of pain relies on a mechanistic understand of its underlying processes. Data types which can provide information on this understanding include patient-reported outcomes, psychological assessments, neuroimaging and molecular markers, of which examples are shown.



- Integration of data from different populations within a translational quantitative systems pharmacology (QSP) model to support personalized treatment and drug development.
  CNS, central nervous system.

Towards personalized treatment of pain using a quantitative systems pharmacology approach

Sebastiaan C. Goulooze[a], Elke H.J. Krekels[a], Monique van Dijk[b,c], Dick Tibboel[b], Piet H. van der Graaf[a,f], Thomas Hankemeier[d], Catherijne A.J. Knibbe[a,e], J.G. Coen van Hasselt[a,*]

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