Dose selection
in early paediatric development

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Clinical Pharmacology Modelling & Simulation

Outline

- Decision tree for the clinical programme
  - Bridging studies
  - PKPD and Efficacy studies

  (***location and shape*** of the exposure-response curve)

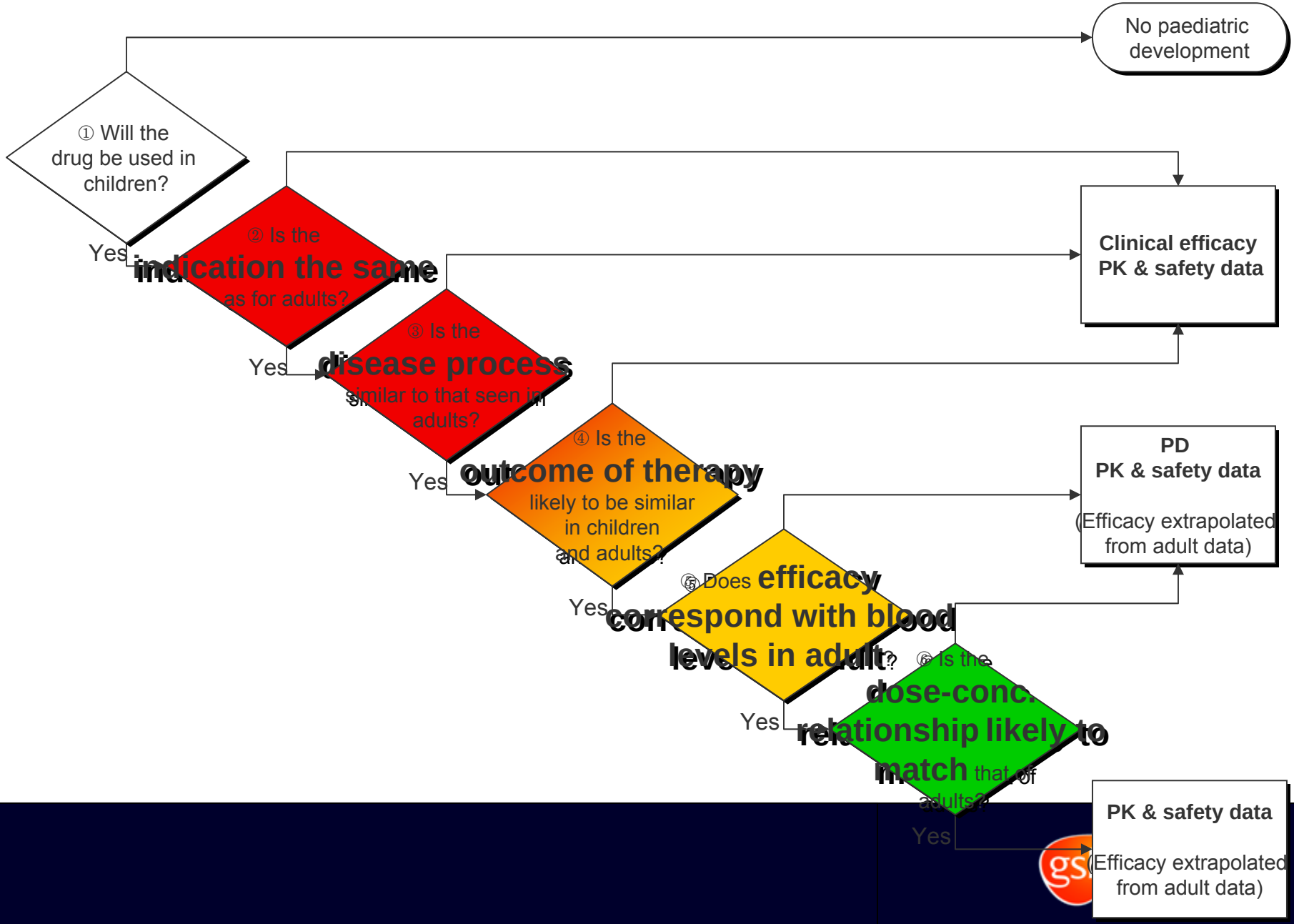
- Recent experience - First time in children
  - ***scaling for function not for size!***

- Cultural and scientific bias
  - demographic covariates *versus* PKPD relationships

- Relevance of a model-based approach
  - integration of adult data
  - consideration about paediatric issues during the development programme in adults

- Conclusions

Paediatric development strategy



Experience in Early Paediatric Development

Indication /Study objective	Age	Dose in adults	Dose in children
RLS - Open label, single dose, dose rising, multi-centre study to assess the tolerability and PK of **Ropinirole** in adolescent patients	**12-17 years old**	**0.25mg**	**start dose 0.125mg (0.25 mg if 0.125 well tolerated)**
Seasonal Rhinitis - Double blind comparison of **Fluticasone Propionate** aqueous spray in children	**4-11 years old**	**200ug od**	**100 /200 ug od**
Seasonal Allergic Rhinitis (SAR) - A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Once-Daily, Intranasal Administration of **GW685698X** Aqueous Nasal Spray in children	**2 to <12 years**	**100 mcg**	**50 & 100 mcg**
Migraine - Long-Term Safety Study of a Combination Product Containing **Sumatriptan** Succinate and **Naproxen** Sodium in Adolescents	**12-17 years old**	**100mg sumatriptan/ naproxen 250-500mg bd**	**85mg sumatriptan in combination/Naproxen 500mg**
Chemotherapy Antiemetic - An evaluation of the pk properties of IV O**ndansetron** in children	**4-18 years**	**0.15mg/kg - 3 daily doses at 4 hour intervals**	**0.15mg/kg - 3 daily doses (4 & 8hrs after initial dose)**
VZV infection - An open-label, multiple-dose, multicenter, pharmacokinetic, safety and tolerability study of **Valaciclovir** oral suspension in infants and children	**1 - <12 years**	**1000 mg**	**20mg/kg - 3 times daily**
Eosinophilic esophagitis - A randomised, double-blind, parallel group clinical trial to assess safety, tolerability, PK and PD of **mepolizumab** (SB240563) (0.55mg/kg, 2.5mg/kg or 10mg/kg) in pediatric patients	**2-17 years**	**Single IV dose up to 100mg/kg - many patients have received up to 10mg/kg**	**0.55, 2.5, or 10mg/kg**
Anticoagulant - Open label study of **Argatroban** injection to evaluate the safety and effectiveness in pediatric patients requiring alternatives to Heparin	**Birth - 16 years**	**initial bolus 250-300ug/kg then 20ug/kg/min**	**initial bolus 100-250 ug/kg then 2 - 3ug/kg/min depending on reason for dosing e.g. cardiac surgery**

Key messages

1. The rationale for dosing regimen in clinical trials is often determined by empiricism. Most importantly, medical practice assumes linear relationships between body size, physiological function and clinical response. There is sufficient clinical evidence to revisit this assumption.

2. Current ICH guidelines for age strata ignore important aspects such as incidence of disease, homeostatic mechanisms and (patho)physiological changes which occur within or across the proposed boundaries.

3. Understanding of disease and PKPD relationships should underpin the rationale for dose selection *before* assigning covariates to adjust for the potential effect of developmental growth on pharmacokinetics, pharmacodynamics and response.

4. Rigid protocols do not meet the needs of this vulnerable population. Flexible study designs are required to ensure optimisation of dosing regimen in early paediatric studies.

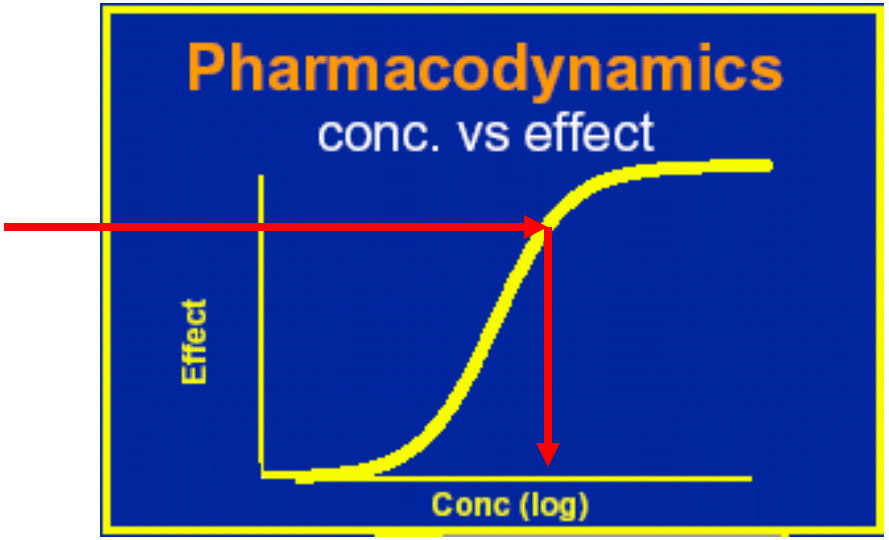
ICH Preferences

- **Age strata:**
  - pre-term neonate (<37 weeks gestation)
  - term neonate (0-27 days)
  - infants & toddlers (28 days to 23 months)
  - children (2-11 years)
  - adolescent (12-18 years)

- **Dosing preference:**
  - mg/kg


SULFANILAMIDE
SULFANILAMIDE
WHAT IS THE APPROPRIATE DOSE?
WHAT IS THE APPROPRIATE SCALING FACTOR ?

Empiricism: problems



DOSE → ? → CONC → EFFECT

Approaches for Scaling of Dose

Covariates in PKPD relationships

- Age [DOSE = f (θ*age)] mg/year
- Body Surface [DOSE = f (θ*BSA)] mg/m^2
- Weight [DOSE = f (θ*weight)] mg/kg
- Allometric scaling (power function)

  [DOSE = f (θ*$(wt_i / wt_{std})^y$]
- No Normalisation [DOSE = Adult dose]

What is Allometry?

- From Greek αλλο μετρον (allo metron, ‘other measure’)

- Originally, allometry was first used to define the relationship between *size* and *basal metabolic rate* (Kleiber, 1932). He proposed the formula

$$BMR = 73.3 * W^{0.75}$$

Where BMR is basal metabolic rate, W is weight, 73.3 and 0.75 are two constants (respectively the allometric coefficient and the allometric exponent)

Dose recommendation for marketed drugs with paediatric indication *vs.* dose adjustment based on allometric scaling

brand name	*active substance*	*adult dose (mg, 70 Kg)*	*paediatric dose (from studies)*	*WEIGHT (Kg)*	*dose (mg)*	*allometric dose (calculated with b=0.75)*	*difference*
EMADINE	emedastine (1 drop = 1/12 ml)	0.083	0.083	20	0.083	0.032	-61%
				30	0.083	0.044	-47%
				40	0.083	0.055	-34%
EMTRIVA	emtricitabine (HIV)	240	6 mg/Kg	10	60	56	-7%
				20	120	94	-22%
				30	180	127	-29%
				40	240	158	-34%
ENBREL	etanercept (Rheumatoid arthritis)	25	0.4 mg/Kg	10	4	5.8	45%
				20	8	9.8	22%
				30	12	13.2	10%
				40	16	16.4	3%
EPIVIR	lamivudine (HIV)	300	4 mg/Kg	10	40	70	74%
				20	80	120	50%
				30	120	160	33%
				40	160	200	25%
EXJADE	deferasirox (thalassaemia)	1400 (20 mg/Kg)	20 mg/Kg	10	200	325	63%
				20	400 (UP)	550	38%
				30	600 (UP)	740	23%
				40	800	920	15%

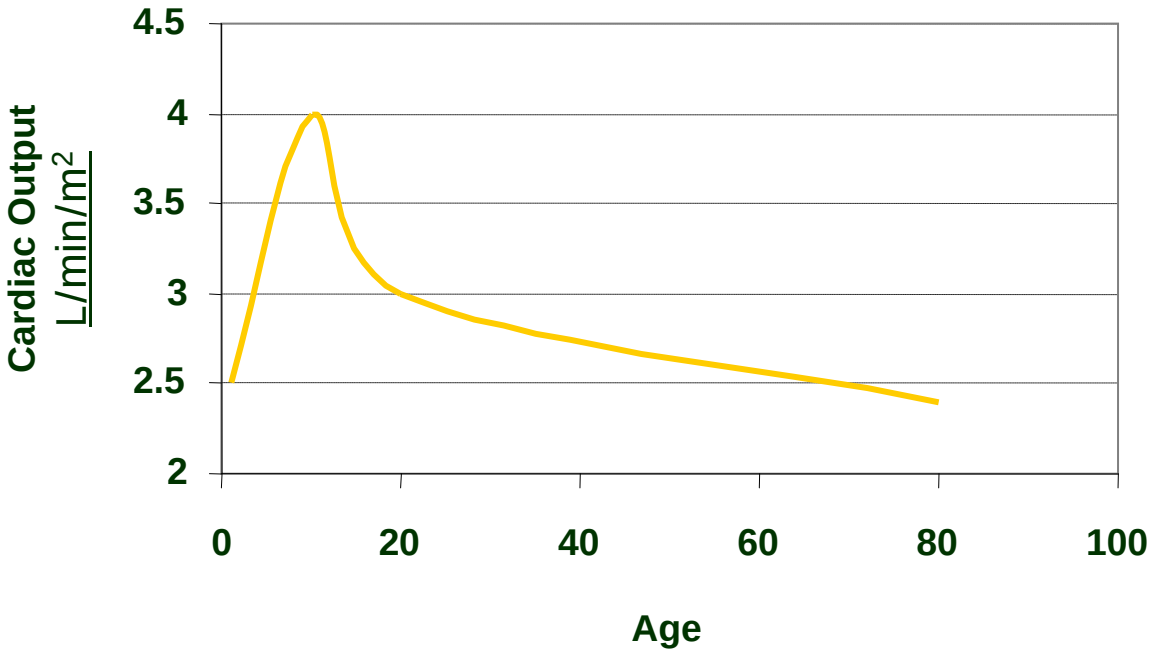
Differences in Exposure and Response

- **Anatomy/Physiology**
  - Structure & function
  - Homeostasis
- **Disease**
  - Co-morbidities
- **Pharmacodynamics**
  - Sensitivity
- **Pharmacokinetics**
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- **Pharmaceutics**
  - Formulation and delivery

Physiology: LBF & Cardiac Output

The size of the liver relative to total body weight decreases from infancy to adolescence.

Liver blood flow (as a proportion of cardiac output) changes with body size (and hence age):



Co-morbidities

Paediatric Bipolar Disorder and ADHD

Comorbidities have impact on:

- **Inclusion and exclusion criteria**
- **Different AE profile from adults**
- **Different Effect size and variability**
- **Drug-drug interactions**

TABLE 2. Scores on Measures of Mania and Attention Deficit Hyperactivity Disorder (ADHD) Severity for Patients With Pediatric Bipo… fects of Treatment Wit…

Study Phase and …	… With … esponse … ng to … vement …[b]	%
Open-label trial[c]		
Baseline (N=40 …		
Last visit while …		7.5
Crossover trial[d]		
Last visit while … divalproex so…		89.6
Last visit while … (N=30)[f]		10.0

[a] Treatment resp…
[b] Treatment response was indicated by a CGI improvement score of 1 or 2.
[c] Patients received 8 weeks of treatment with open-label divalproex sodium (median dose=750 mg/day at the end of the open-label phase).
[d] Patients with a ≥50% reduction in the baseline Young Mania Rating Scale score at the end of the 8-week open-label phase were randomly assigned to receive, in addition to divalproex sodium, either mixed amphetamine salts (5 mg by mouth b.i.d.) or placebo for 2 weeks under double-blind conditions and then the alternative treatment (in addition to divalproex sodium) for 2 weeks.
[e] N=29 for CGI improvement score for ADHD symptoms.
[f] N=28 for Young Mania Rating Scale score.

Bipolar II disorder	9	22.5	8	26.7

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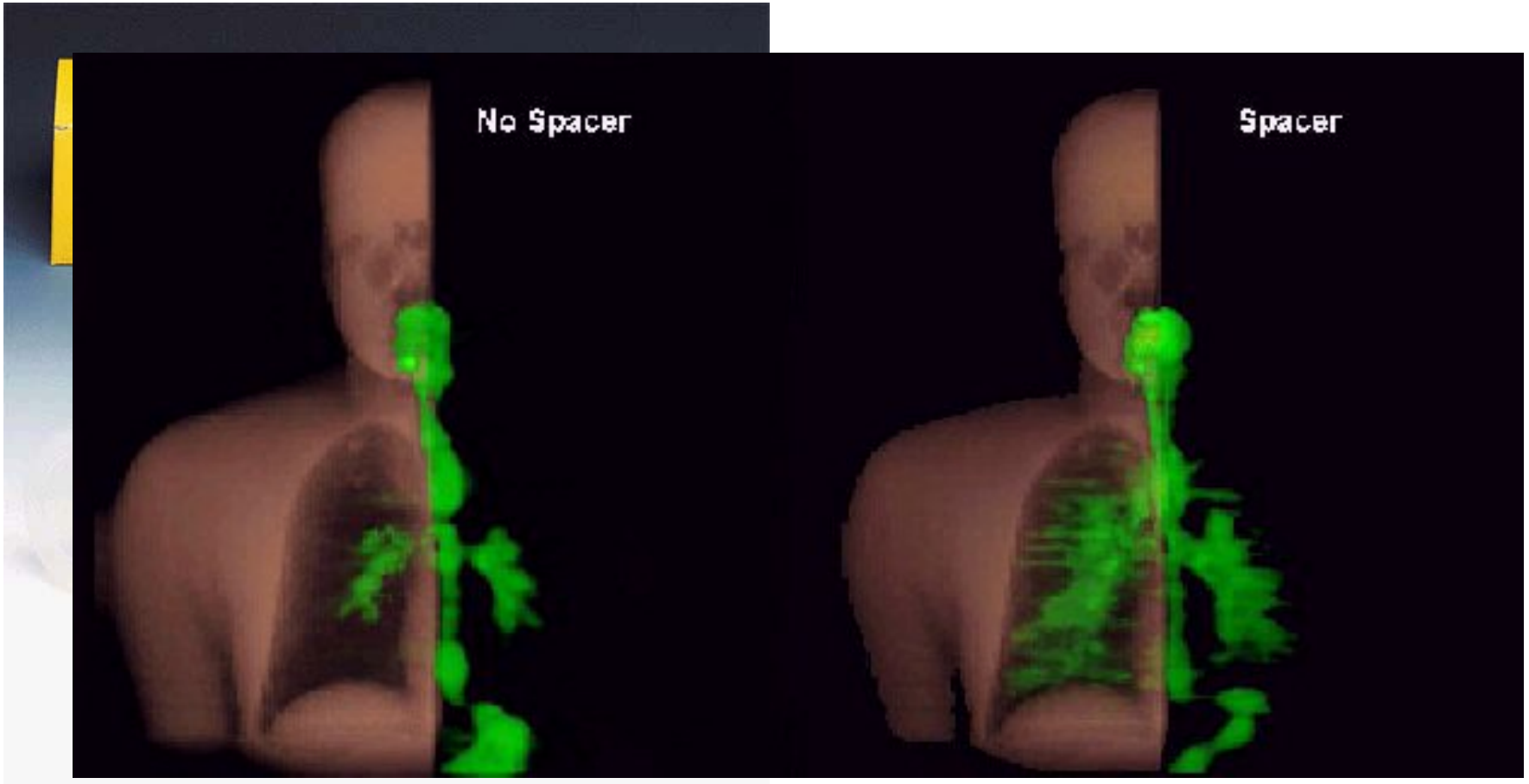
Factors affecting rate and extent of absorption

Inhaled drugs



Operational Considerations
Study Design

- Staggered X Sequential Paediatric Programme
- Chronic X Acute Indication
- PK Differences Only
- Different PK/PD Relationship and AE profiles

Operational Considerations
Study Design

- Clinical endpoints
  - validation of assessment scales
  - tailored equipment

- Sampling techniques
  - sparse population sampling
  - sensitive assays
  - collection methodology
- Data Analysis

"Bridging" Studies

- Criteria for extrapolation from adult data
  - same indication as adults
  - disease process similar to adults (i.e., similar PKPD relationships)
  - outcome of therapy likely to be comparable

- In addition:
  - **PK in adult patient population** available

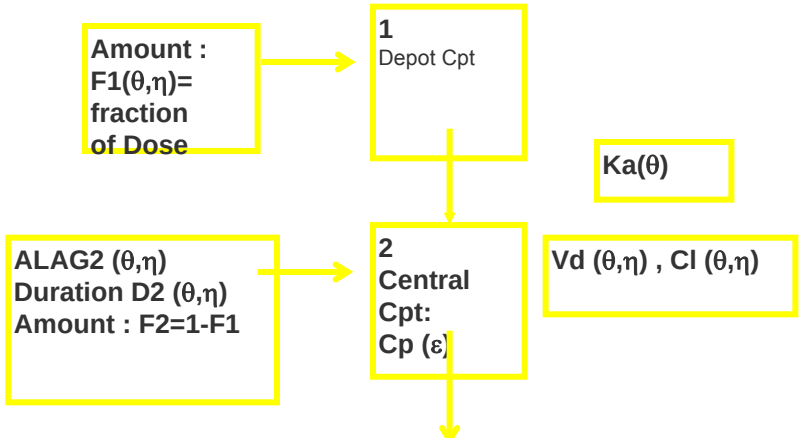
Sumatriptan for Migraine Attacks in adolescents and children

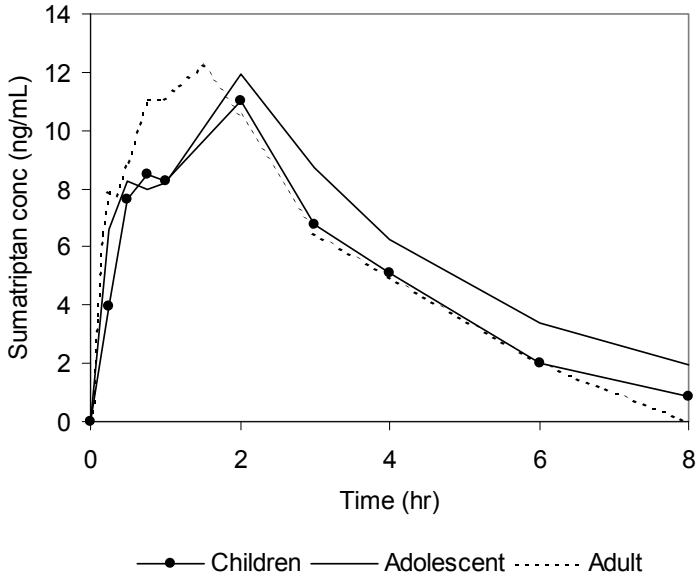
Similar exposure to adult migraineurs treated with 20mg sumatriptan nasal spray

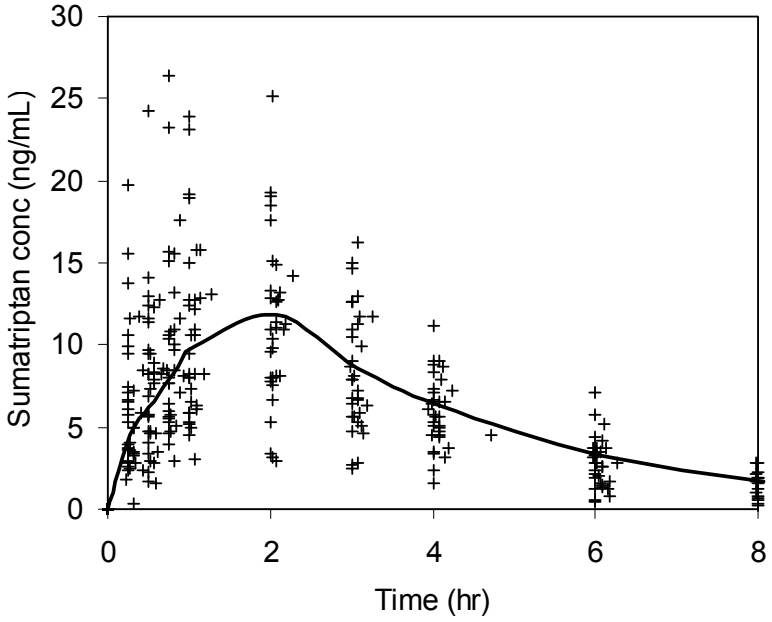
- 9, 10 or 11 years of age
  - **10** mg of sumatriptan NS unless weight > 40 kg
  - children with weight > 40 kg: **20** mg.
- 6, 7 or 8 years of age
  - **5** mg of sumatriptan NS unless weight > 25 kg
  - children with weight > 25 kg: **10** mg.

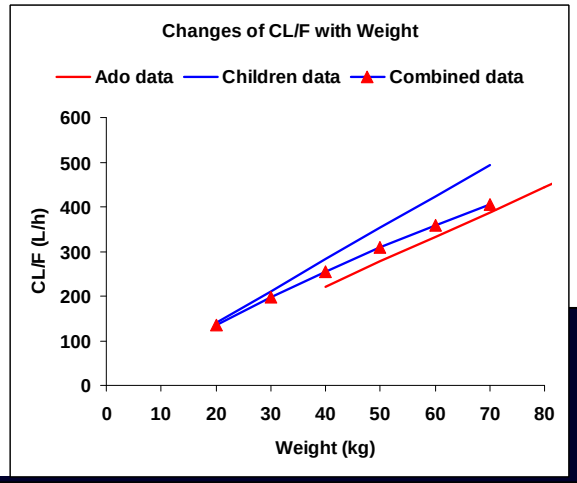
Christensen M, Mottern R, Jabbour J, Fuseau E.
Pharmacokinetics (PK) of sumatriptan nasal spray in adolescent migraineurs. Clin Pharmacol Ther 2000;67(2):103.
Intranasal Sumatriptan (IS) Pharmacokinetics (PK) in Child Migraineurs Eur Clin Pharmacol Ther 2001

PK model (common to all populations)









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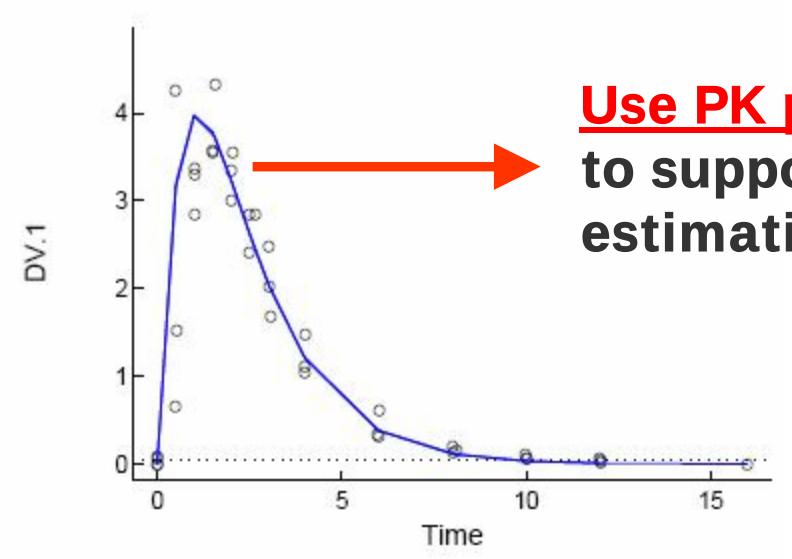
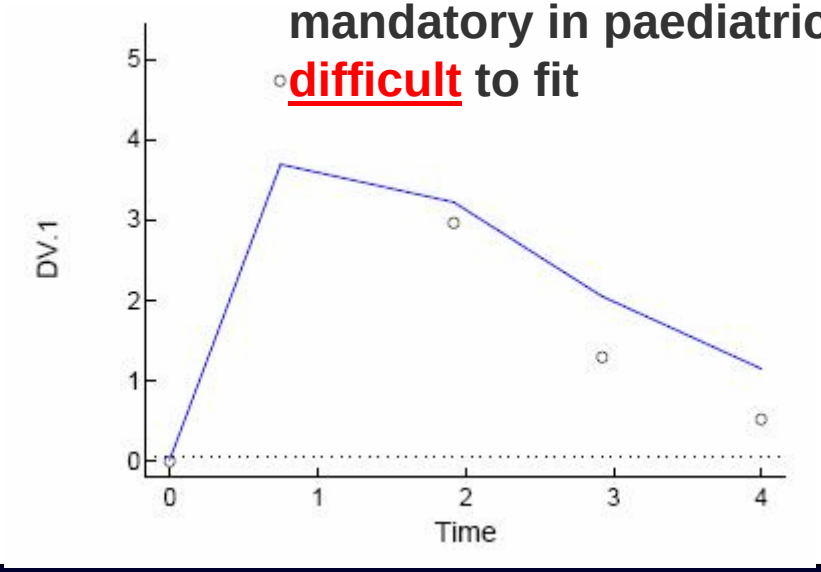
Incorporation of priors (adult PK) - Bayesian hierarchical models -



Use PK parameters in adults to support parameter estimation in children

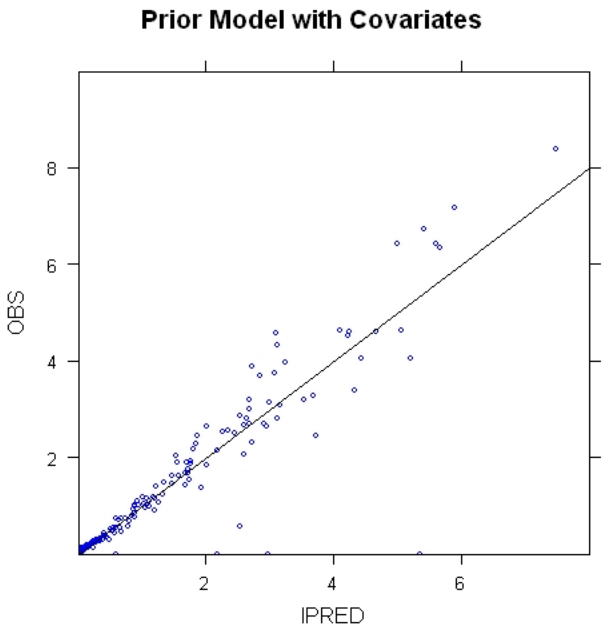
Sparse sampling scheme, mandatory in paediatrics, difficult to fit

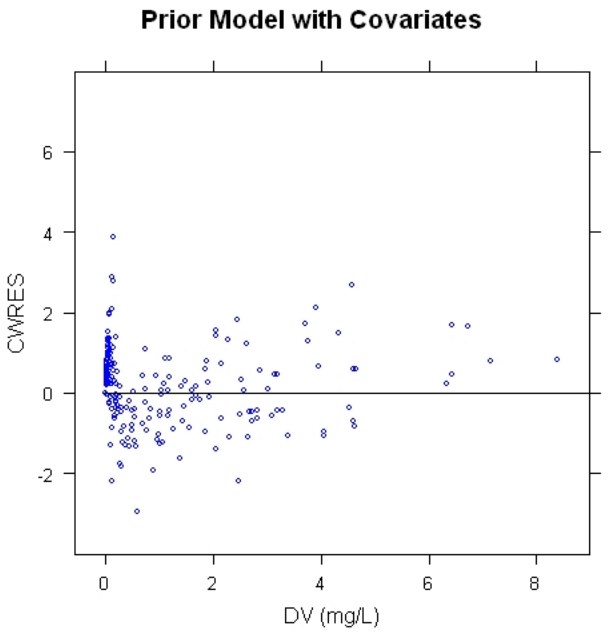


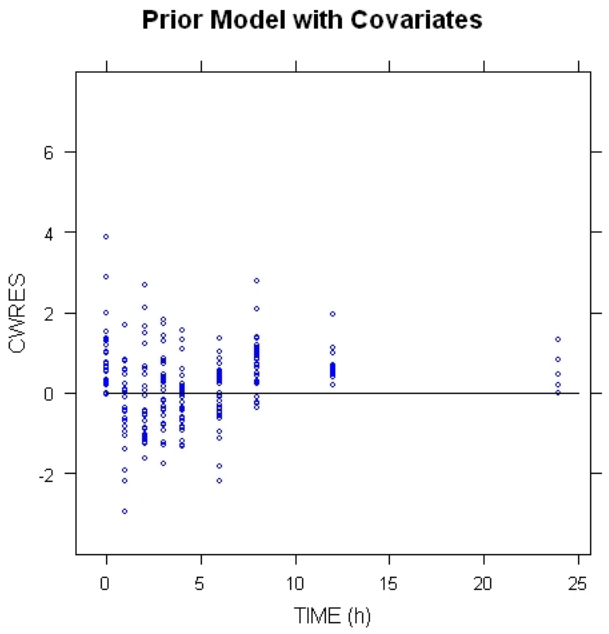
Priors can also contribute to characterising whether estimates originate from the same parameter distribution

Incorporation of priors (adult PK) - Bayesian hierarchical models -

Example of analysis in HIV

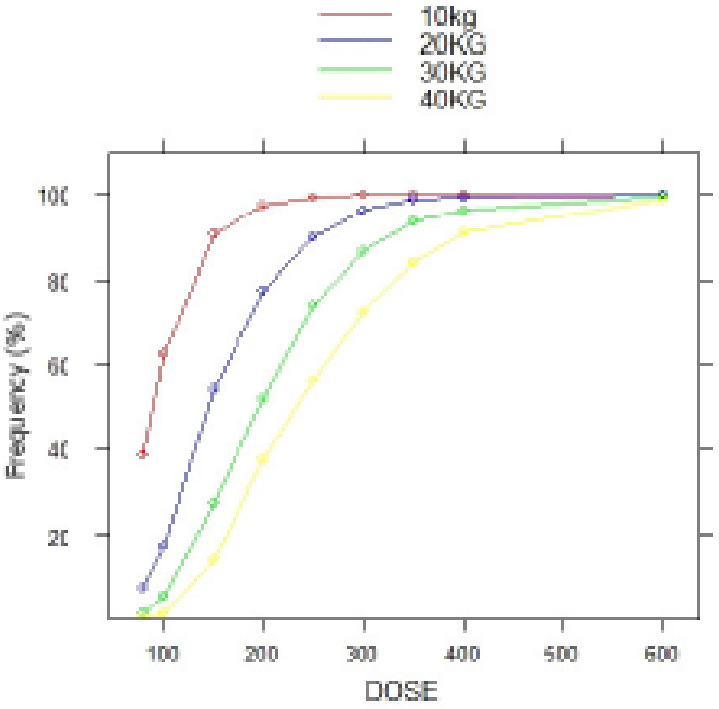






Incorporation of priors (adult PK) - Bayesian hierarchical models -

In a bridging study for the HIV indication, dose adjustments are aimed at achieving exposure equivalent to the reference population (i.e., adults). Model-predicted exposure (AUC) for doses of antiviral therapy, which are required to achieve the median adult exposure



Weight (Kg)	*Predicted dose (mg)*
10	120
20	200
30	260
40	320

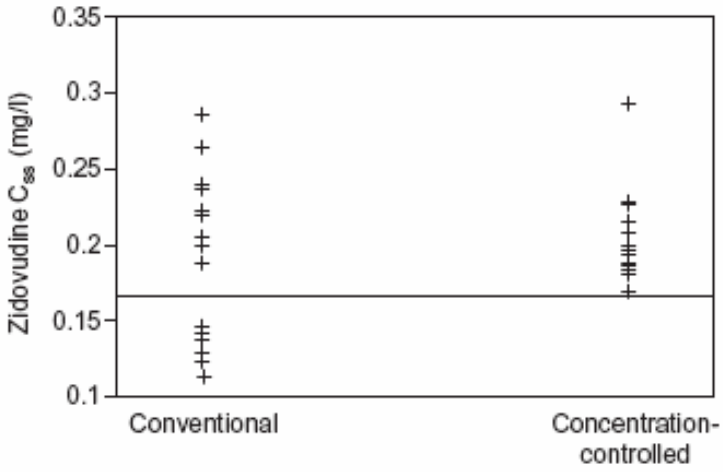
PKPD and Efficacy Studies

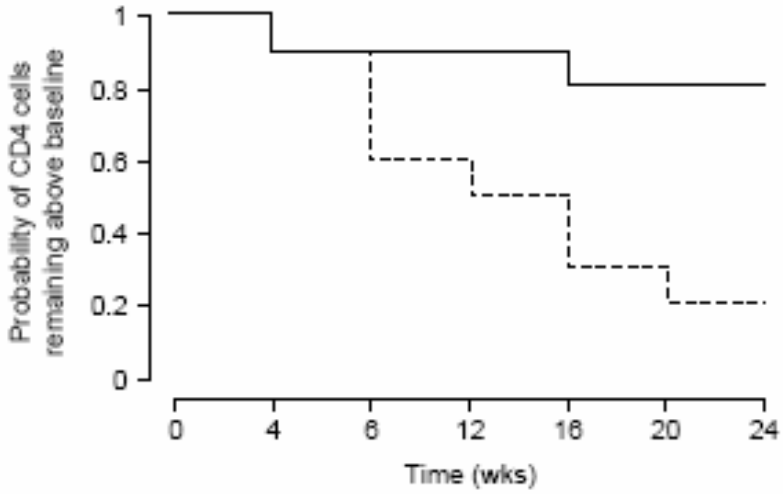
There are design possibilities that may be more efficient, i.e., giving a surer answer about the location & shape of the exposure-response curve, providing important data for subsequent regulatory studies.

These include:

- Enrichment approaches - larger effect sizes give surer answers
- Better dose finding - a useful titration design (Sheiner) and attention to dose throughout Phase III
- Reversing the sequence - the randomised withdrawal study

Is RCCT an effective Approach?





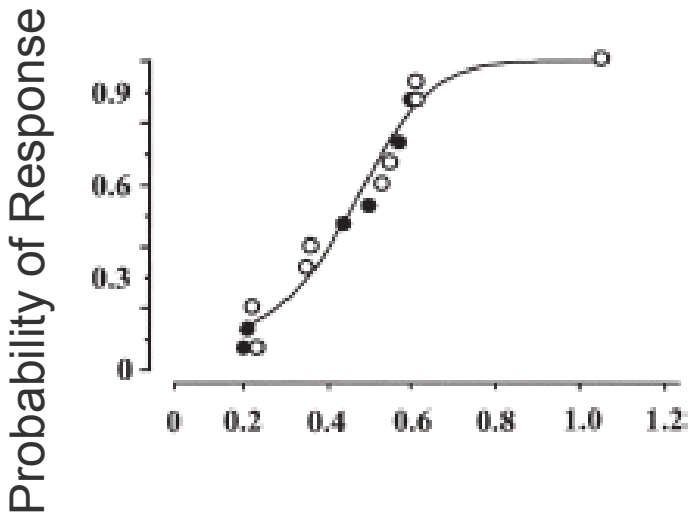
Outcome of antiviral therapy with zidovudine in patients with HIV, comparing RDCT with RCCT. Study duration 52 weeks with PK assessment at week 2 and dose adjustment at week 4,

The Kaplan-Meier survival analysis for the probability of CD4+ cell counts remaining above 90%of the baseline value shows a significantly superior response in the group of patients who were assigned to a target concentration of 0.17 mg/L or greater compared with patients assigned to the 300 mg BID standard dosage.

Fletcher CV, Acosta EP, Henry K, et al. Concentration-controlled zidovudine therapy. Clin Pharmacol Ther 1998; 64: 331-8

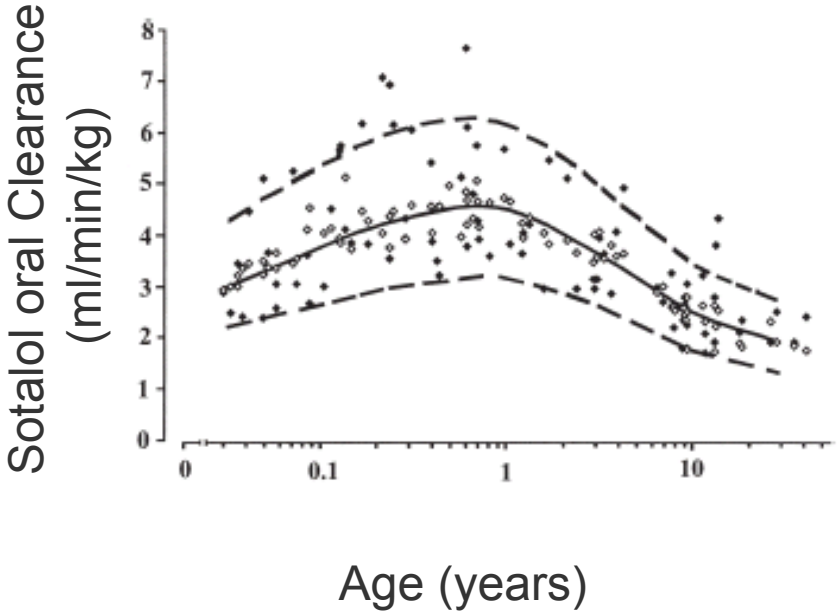
PKPD Modelling - Sotalol in SVT

PK/PD relationship



Probability of arrhythmia suppression in the 15 children with supraventricular tachycardia vs sotalol trough concentration under steady-state conditions and an 8-h dosing interval.
Filled circles 6 neonates (28 days).

Effect of Age on Clearance



Measured **(closed diamonds)** and model predicted oral sotalol clearance based on body weight **(open diamonds)**. Median **(solid line)** and the 10th and 90th percentile **(dashed line)** of 1,000 simulated data sets.

Läer S, Elshoff JP, Meibohm B, Weil J, Mir TS, Zhang W, Hulpke-Wette M.
J Am Coll Cardiology 2005 46(7):1322-30.

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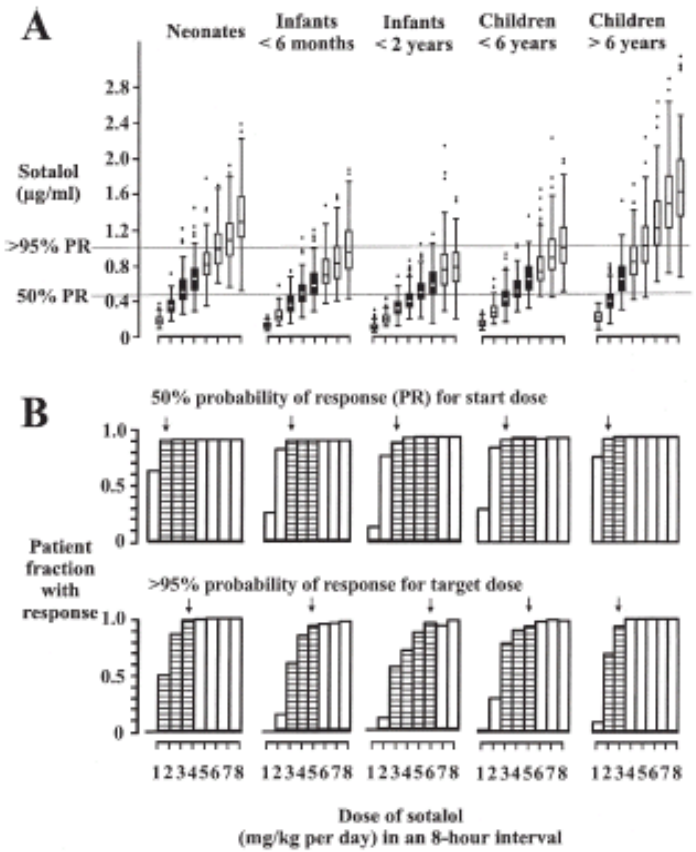
Dose Recommendation



Age-specific Dose regimen for sotalol in Children with SVT

Group	8-h Dosing Interval: Optimized Dose of Sotalol According to the Trial Simulation (Start/Target) (mg/kg/day)	8-h Dosing Interval: Recommended Clinically Useful Dose of Sotalol (Start/Target) (mg/kg/day)
Neonates	2/4	2/4
Infants <6 months	3/5	3/6
Infants <2 yrs	3/6	3/6
Children <6 yrs	3/5	3/6
Children >6 yrs	2/3	2/4

Black box plots and **hatched bars** indicate recommended dosing range. **(A)** Simulated sotalol trough concentrations (125 patients per group and dose level) for paediatric patients with supraventricular tachycardia. **Lines** indicate 50% and more than 95% efficacy. **(B)** Patient fraction with 50% and more than 95% probability of arrhythmia suppression. **Arrows** indicate start and target doses.

Summary

- Decision tree for the clinical programme
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  (***location and shape*** of the exposure-response curve)

- Recent experience - First time in children
  - ***scaling for function not for size!***

- Cultural and scientific bias
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  - integration of adult data
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Conclusions

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