Population Modelling of the Absolute Bioavailability and Pharmacokinetics of Phenobarbitone in Infants with Seizures

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Neonatal Seizures

- Seizures arise from an electrophysiological imbalance in brain; Neuro-excitatory activity exceeds neuro-inhibitory activity
- Seizures occur more often in the neonatal period then at any other time in life
- Incidence of 1-2 per 1000 term live births
- Higher risk (6%-13%) in premature infants
- Diagnosis by clinical observation, confirmed in majority of cases by EEG

Neonatal Seizures - Concerns

- Seizures are a neurologic condition requiring *immediate* medical attention
- Repetitive/prolonged neonatal seizures can increase susceptibility of developing brain to subsequent seizure-induced brain injury in adolescence/adulthood (changed neuronal connectivity, not cell death)
- Overzealous a/c medication may contribute to brain injury in continuing seizures

Neonatal Seizures - Treatment

- Phenobarbitone (PB) is a mainstay of treatment; PB doses adjusted to a putative target therapeutic range of 15-25 mg/L
- Low PB levels: Breakthrough seizures; Asphyxia during seizures → hypoxemia
- High PB levels: Delay development in otherwise non-seizure children (brain injury 2^{o} to hypoperfusion)
- Weaned of PB after 1-3 months seizure-free

Drug Absorption in Infants, Neonates

- Infants, neonates – Rate of and extent of drug absorption may vary from older children and adults because of several factors including;
  - Gastric and duodenal pH
  - Gastro-intestinal emptying/motility
  - Pancreatic and bile secretions
  - Intestinal absorptive surface area
  - Intestinal mucosal barrier function

- Very little data on PK of phenobarb in neonates and infants, while bioavailability of PB is unknown

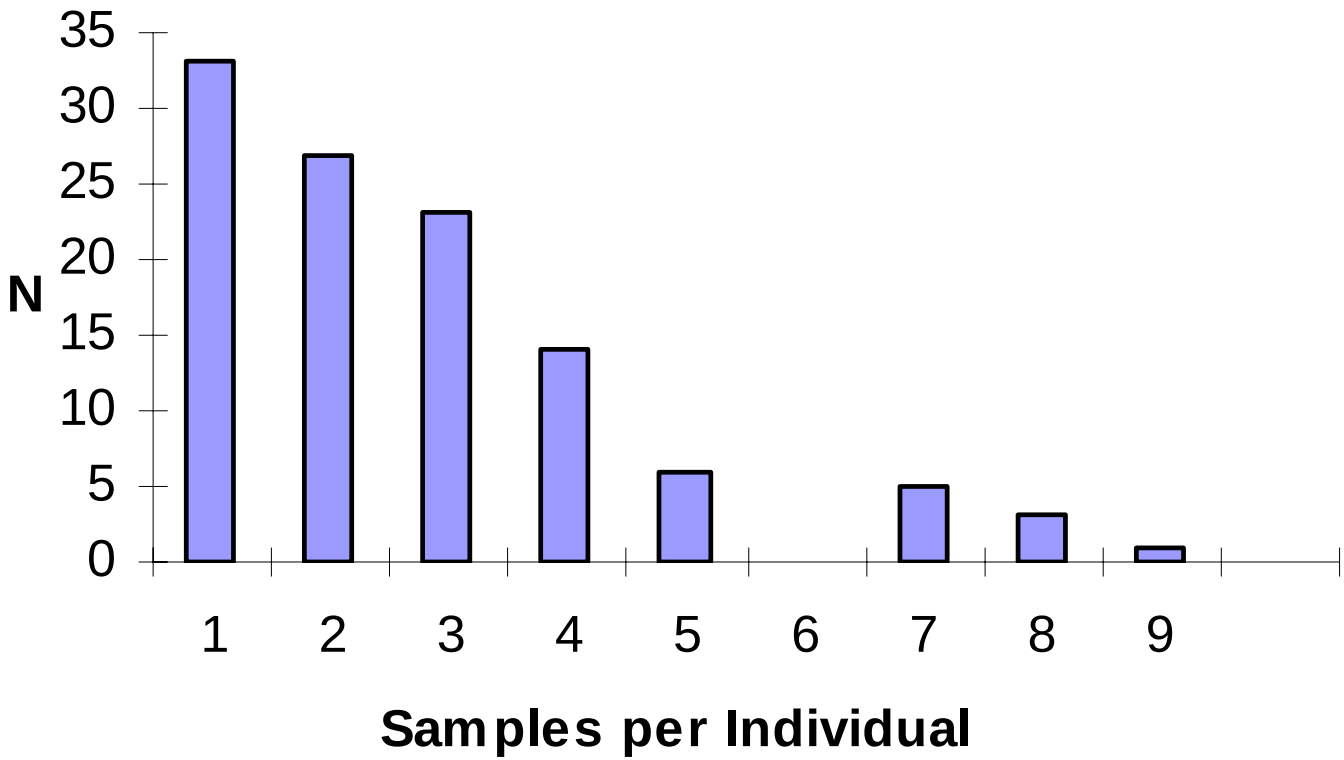
Study Aims

- To determine *clearance, volume of distribution, oral bioavailability* of phenobarbitone in neonates and infants
- Assess the influence of various patient characteristics on the PK typical values
- Estimate the interindividual *variability* about PK parameters, and the residual variability in the population model

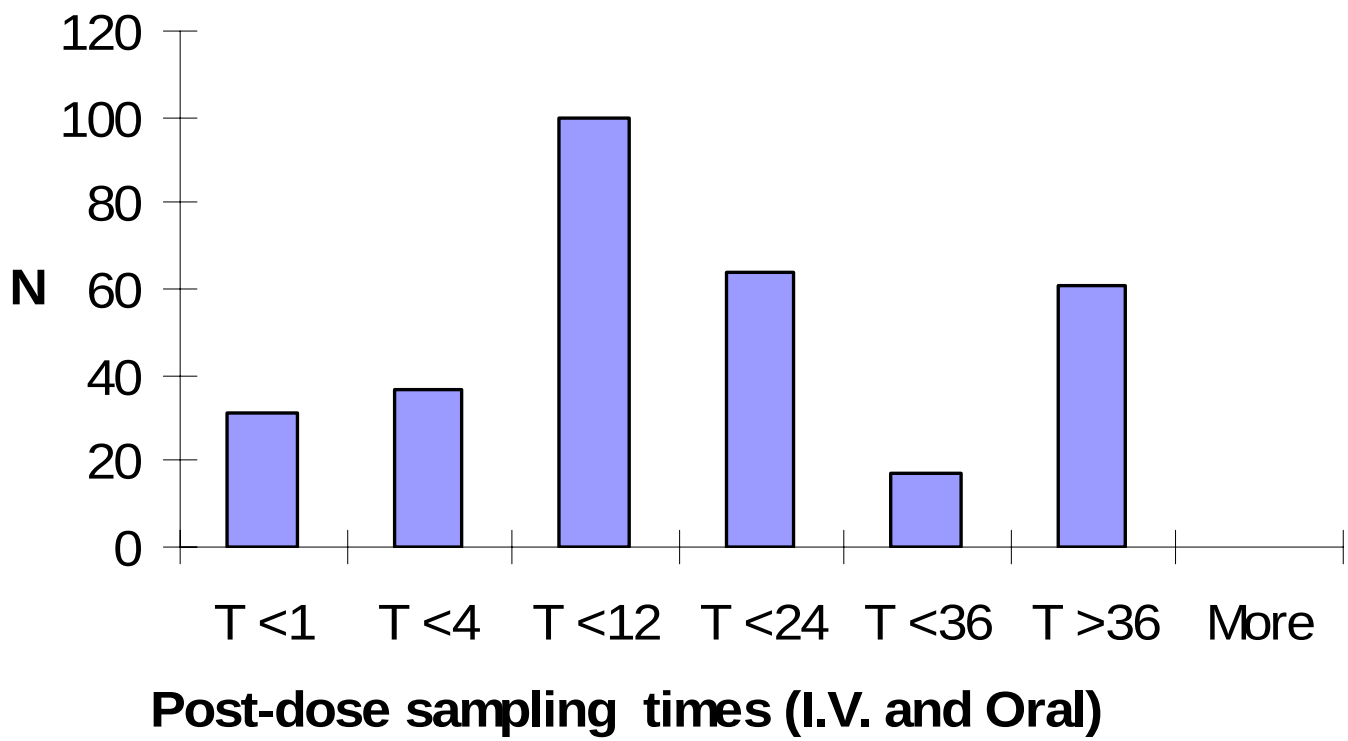
Patient Characteristics

Patients (M, F)	113	(73,40)
Weight (kg)	3	(0.59-5.8)
Gestation age (weeks)	37	(23-42)
Postnatal age (days)	13	(1-108)
Samples (i.v., p.o)	310	(183,127)
Samples per individual	2	(1-9)
PB conc. (mg/L)	30	(3-93)

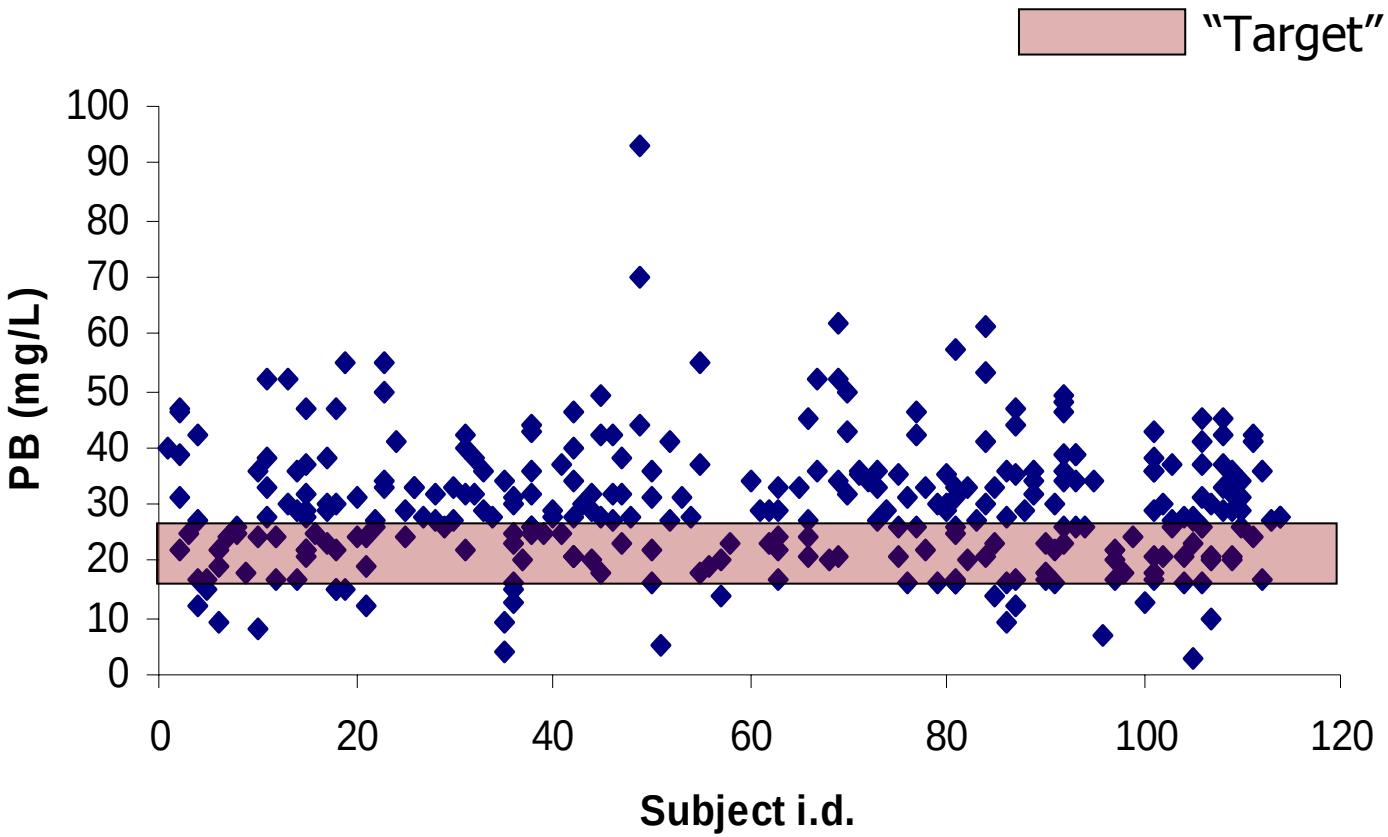
Samples per Individual



Sample Times – I.V. and Oral



Raw Data


"Target"
PB (mg/L)
100
90
80
70
60
50
40
30
20
10
0
0
20
40
60
80
100
120
Subject i.d.

Methods

- Retrospective TDM serum phenobarb data
- NONMEM 5 (v.1.1), G77 compiler
- ADVAN2 TRANS2
- Covariate screening (P=0.01, ΔOFV -6.7)
- FOCE with INTERACTION (η and ε)
- Variability; BLOCK (CL, V, F1)

$$P_{k_j} = P_{k_{TV}} \cdot e^{\eta_{j,P_k}}$$

$$C_{OBS,ij} = C_{PRED,ij} + \varepsilon_{ij}$$

Examples of Covariate Screening

	ΔOFV	
Clearance (CL)		
Weight	-50	
Age	-18	
Gestational age	-10	
Sex	194	
Infection	5	
Weight + Age	-83	
Volume (V)		
Weight	-53	
Age	14	
Infection	470	
CL (Weight), V (Weight)	-97	(Final)
CL (Weight + Age), V (Weight)	-141	

Population Model

Structural Model

Ka (/h) = **2.0** fixed

CL (L/h) = **0.0122** + **0.00328** (Wt-3270)/1000

V (L) = **1.9** + **0.592** (Wt-3270)/1000

F (%) = **0.61**

Derived

$\mathbf{t_{1/2}}$ (h) = **108**

Variance Model

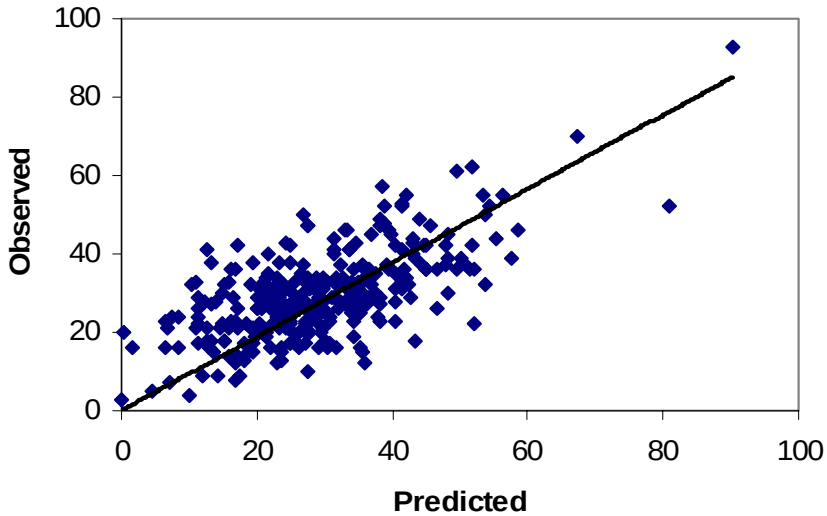
Interindividual variability (CV%)

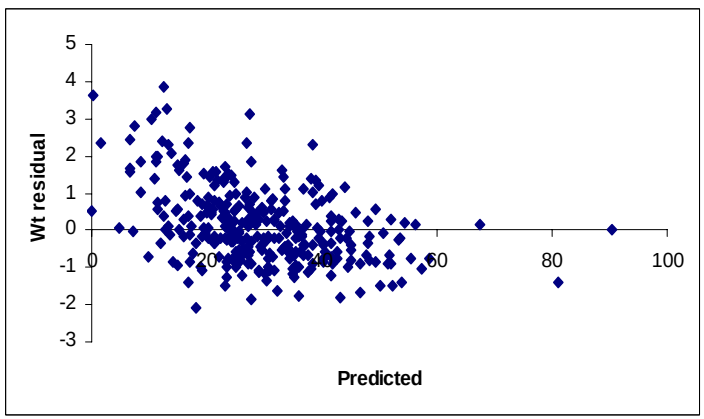
CL	38.0
V	33.9
F	33.6

Residual variability (mg/L)

σ	6.0 (40%-20% at 15-30 mg/L)

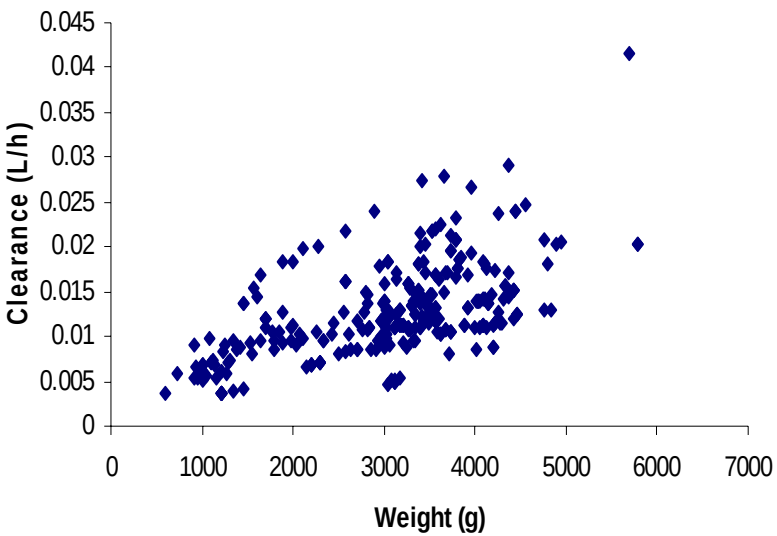
Model Diagnostics

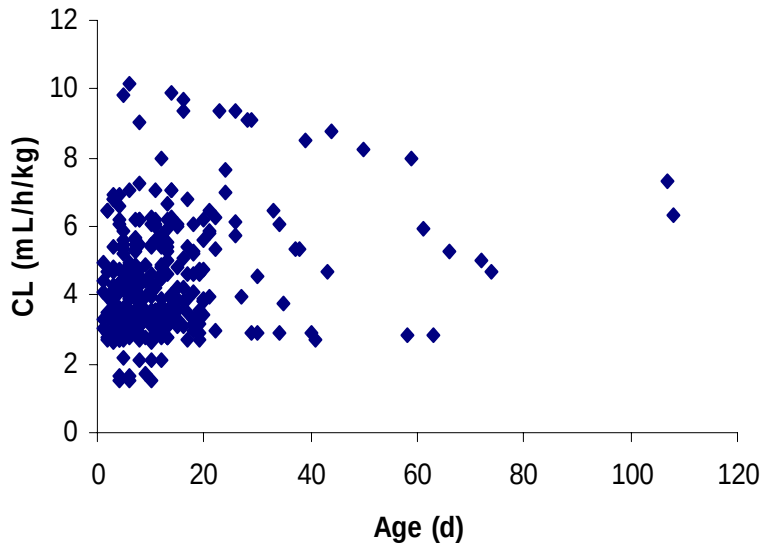




Weight, Age and Clearance

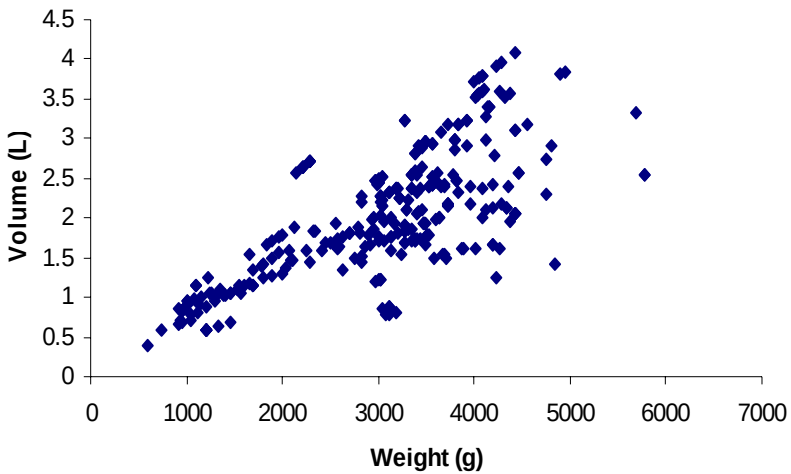
CL (L/h) = 0.0122 + 0.00328 . (Wt – 3270)/1000

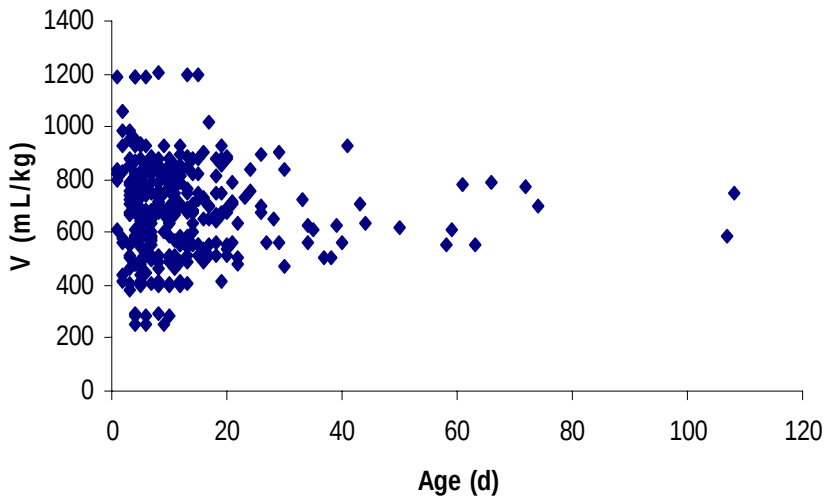




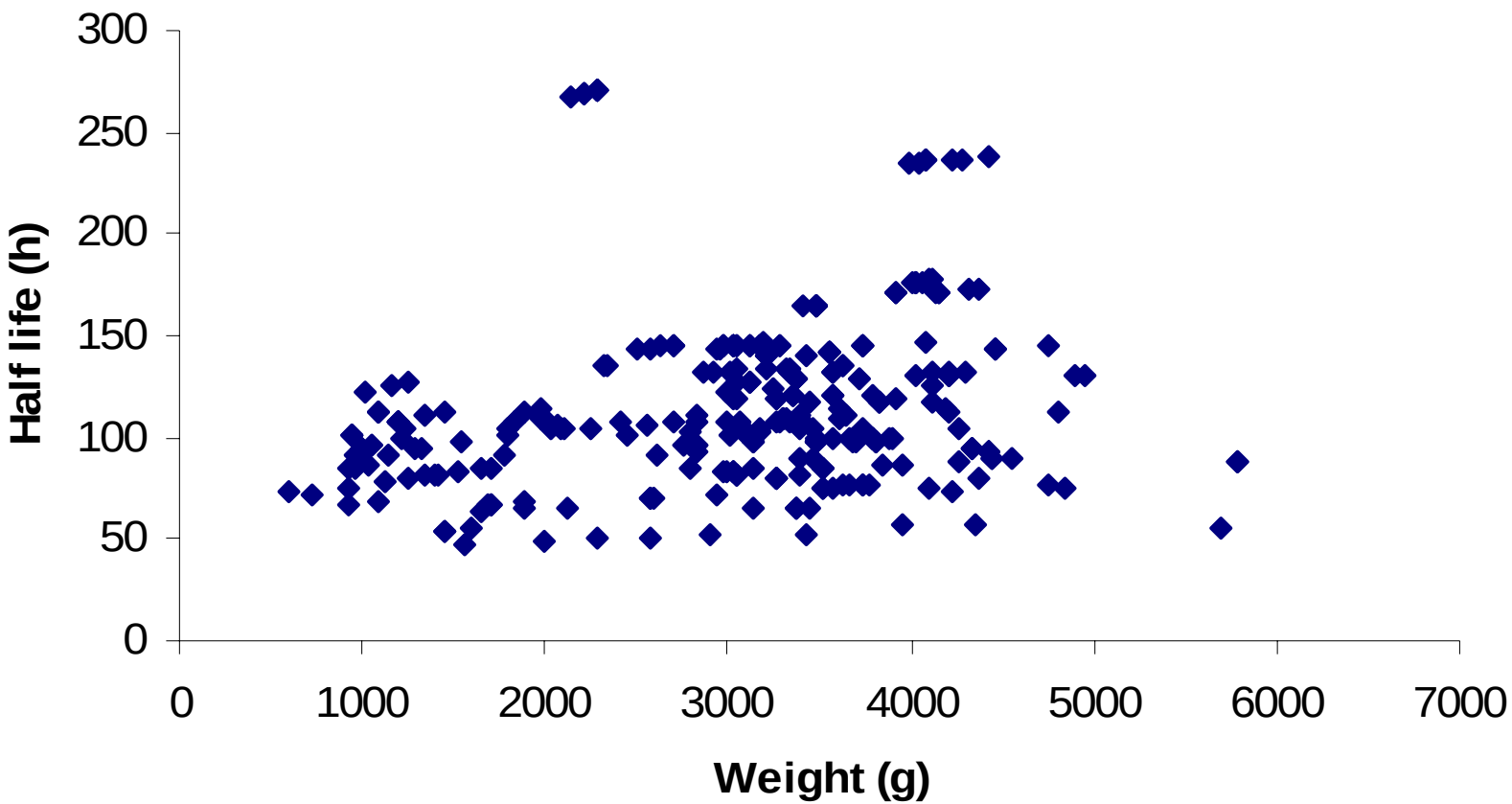
Weight, Age and Volume

$$V\ (L) = 1.9 + 0.592\ .\ (Wt - 3270)/1000$$

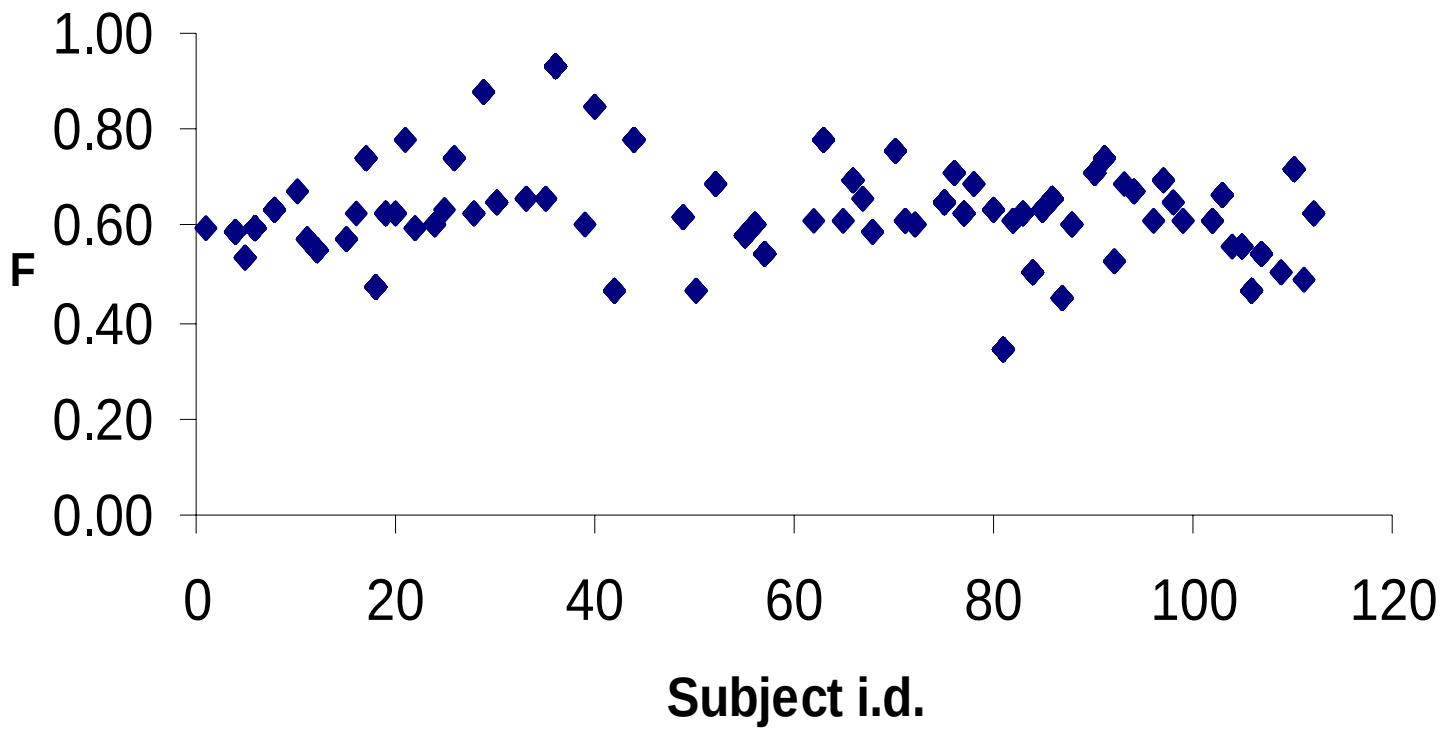




Weight and Half Life



Oral Bioavailability



Phenobarbitone PK – Infant vs Adult

Parameter	Infant*	Adult
Clearance (mL/h/kg)	3.7	3.0 - 4.3
Volume (mL/kg)	581	540 - 700
Half life (h)	108	96 - 100
Bioavailability (%)	61	90 - 100

*At median wt (3270 g), this study

Summary and Conclusions

- CL, V of phenobarbitone increase linearly with weight from birth to 3.5 mo.
- CL per kg, V per kg is constant from birth to 3 mo; CL, V, $t_{1/2}$ similar to adults
- Current practice of LD and MD per kg is OK
- Oral bioavailability is 61%; Implications for switching i.v. <---> p.o.?
- Considerable interindividual variability in PK
- 20%-40% unexplained variability in TR

Some Significant Facts About Australia!

- World's driest continent
- World's shortest Prime Minister
- World's most beautiful women (and men)
- World's best weather, beaches, bla...bla...

and

- The Australian Centre for Paediatric Pharmacokinetics (ACPP)

ACPP - Mater Children's Hospital, Brisbane

Come down and see us sometime!!

8th World Congress on Clinical Pharmacology & Therapeutics, Brisbane, 1st - 6th August, 2004

7th PAGANZ-PAWS meeting, Brisbane, Feb., 2005