

Pharmacokinetics and Pharmacodynamics in Paediatric Therapeutics

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Background

- Pharmacokinetics and pharmacodynamics are very different in children and adults
- PK and PD has a relationship in most drugs in both children and adults

Children are not small adults

- Rapid changes in size, body composition, and organ function that occur during the first year of life
- Adolescents studies reveal complexity in drug metabolism and differences in drug metabolism between the sexes
- An information gap currently exists regarding the developmental and genetic aspects (i.e., the possible role of polymorphisms) of liver enzymes regulation and its potential effect on pediatric drug therapy

What may be the cause

- The growth in liver size does not seem to play a role
- Possibly neuroendocrine determinants of growth and maturation may, in part, be responsible for the observed developmental differences in the activities of certain drug-metabolizing enzymes
 - human growth hormone can modulate the effect of many general transcription factors, the demonstrated regulatory role for growth hormone in the expression of CYP2A2 and CYP3A2 in rats

Issues

- Clinicians and even pharmacokineticists and toxicologists are presented with challenges in prescribing safe and effective doses of therapeutic agents
- Understanding differences in pharmacokinetics due to developmental factors relies on better understanding of the dose versus concentration versus effect profile for a specific drug in patients of various ages

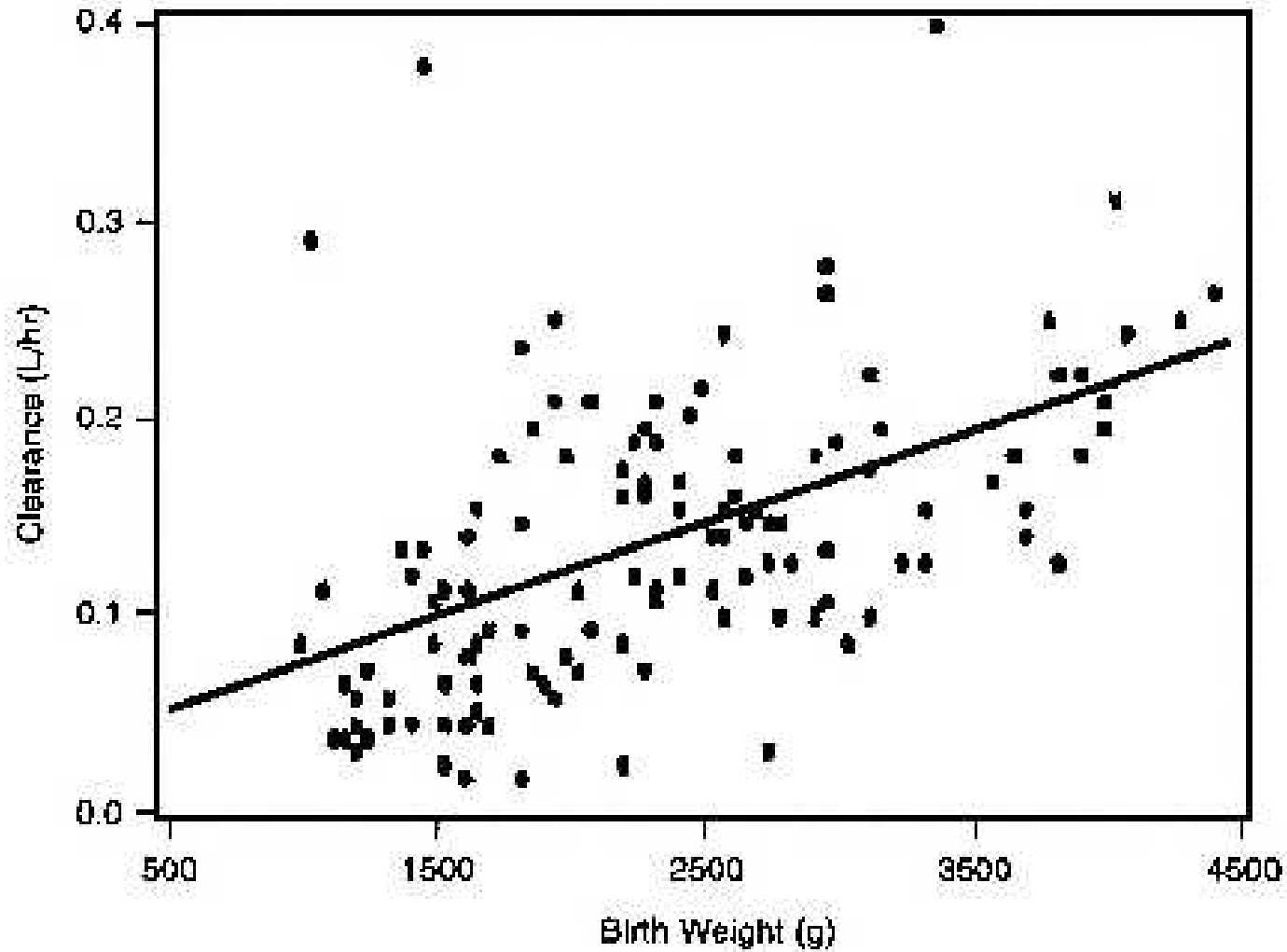
Theophylline

- Elimination half-lives ranged, 9 - 18 hours in term infants 6 to 12 weeks of postnatal age
- Linear relationship between postnatal age and theophylline half-life
- Elimination half life approximately 3 - 4 hours by 48 weeks of life
 - alterations in theophylline plasma clearance occurring between 30 weeks (i.e., approximately 10 ml/h/kg) and 100 weeks (i.e., approximately 80 ml/h/kg) of postconceptional age was primarily the result of age-dependent differences in the metabolism of theophylline by CYP1A2 were dependent pathways

Volume of Distribution

- Phenytoin pharmacokinetic demonstrated an age dependence in V_{\max} , which declined from approximately 14.0 mg/kg/day at 6 months of age to 8 mg/kg/day at 16 years of age
- Ibuprofen in persons aged from 5.5 to 29.6 years demonstrated an inverse linear correlation between age and the apparent oral clearance of the drug

Midazolam clearance in newborns by birth weight



Insight

- Pharmacologic and pharmacokinetic evidence supports the presence of isoform-specific developmental differences in the activities of a host of phase I and phase II drug-metabolizing enzymes
- Pharmacogenetic differences between patients of the same age can have profound effects on drug metabolism (and clearance) by producing quantitatively important differences in the rates and routes of drug biotransformation. Furthermore, the apparent drug biotransformation phenotype may be influenced by disease (e.g., infection), environmental factors (e.g., diet and environmental xenobiotics compounds), and concurrent medications

The gist

- Drug response is a function of the complex interplay among genes involved in drug transport, drug biotransformation, and receptor and signal transduction processes, among others
- Clinical investigations designed to examine pharmacokinetics must include both genotypic and phenotypic assessments so that valid biologic correlates are available to address variability in both drug disposition and, in some cases, drug response

Did you know

- There is a \$3.7 billion market for pediatric medications, compared with an estimated total \$94 billion prescription market for both pediatric and adult therapeutic categories.
- Neurologic products for the adult market are approximately \$7 billion, twice the entire market for pediatric medications.
 - pharmaceutical companies have difficulty in developing pharmaceutical products for the pediatric patient: the therapeutic categories are many and market sizes are small compared to those for the adult market

Child friendly drugs

- Factors that can increase the level of compliance and therefore improve the therapeutic outcome of medications in the pediatric population include dosing flexibility and dose administration.
 - most intranasal products being used for children are not specifically designed for the pediatric patient.
 - the volume of intraocular medications are dosed on the basis of that for the adult eye, which can cause discomfort in the child.
 - Palatability and appropriate dosage forms of oral medications are also important i.e. up to 50 percent of children on oral steroids refuse to take their medicine because of the bitterness associated with these compounds.

Children uniqueness

- Many physiologic differences between children and adults may result in age-related changes in pharmacokinetics and pharmacodynamics.
- Factors such as gastric pH and emptying time, intestinal transit time, immaturity of secretion and activity of bile and pancreatic fluid among other factors determine the oral bioavailability of pediatric and adult populations.
- Anatomical, physiological and biochemical characteristics in children also affect the bioavailability of other routes of administration.

Determinants

- Drug distribution between the pediatric population and adults are membrane permeability, plasma protein binding and total body water.
- Drug metabolism, important differences have been found in the pediatric population compared with adults both for phase I and phase II metabolic enzymes.
- Immaturity of glomerular filtration, renal tubular secretion and tubular reabsorption at birth and their maturation determine the different excretion of drugs in the pediatric population compared to adults.

Gastric pH

- At birth, pH is practically neutral (6-8), then falls to approximately 1-3 within the first 24 after birth and later returns to neutrality by day 10.
- pH slowly declines again thereafter to reach adult values.
- By the age of three years, the amount of gastric acid excreted per kilogram of body weight is similar to that excreted in adults, thus reaching the same pH values
- These initial changes do not occur in prems, who seem to have little or no free acid during the first 14 days of life

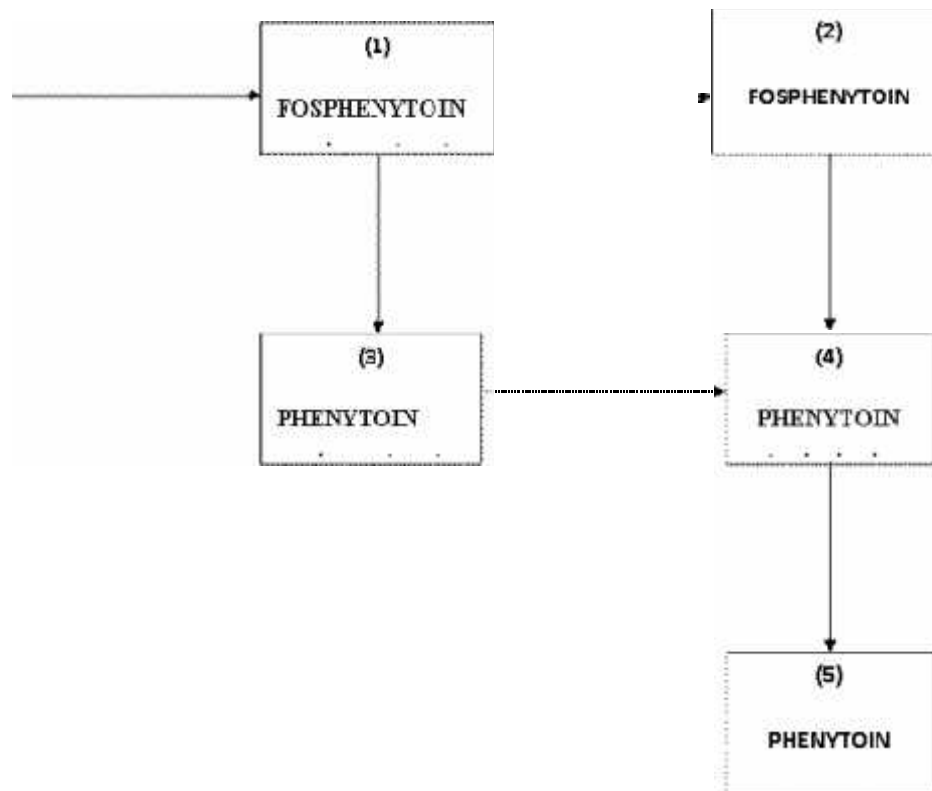
Routes of Administration

- Oral
- IM
- Rectal
- Percutaneous
- Intrapulmonary
- Intranasal
- IV

PK

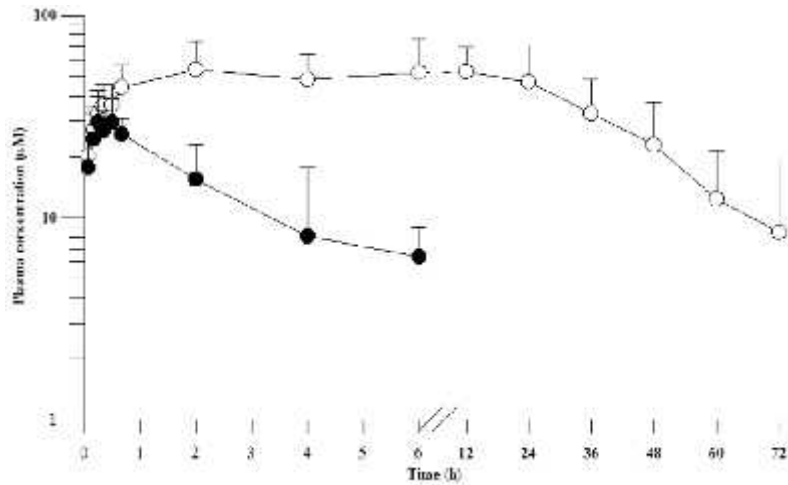
- Distribution
- Membrane permeability
- Protein binding
- Body water
- Excretion

Kinetics determinants

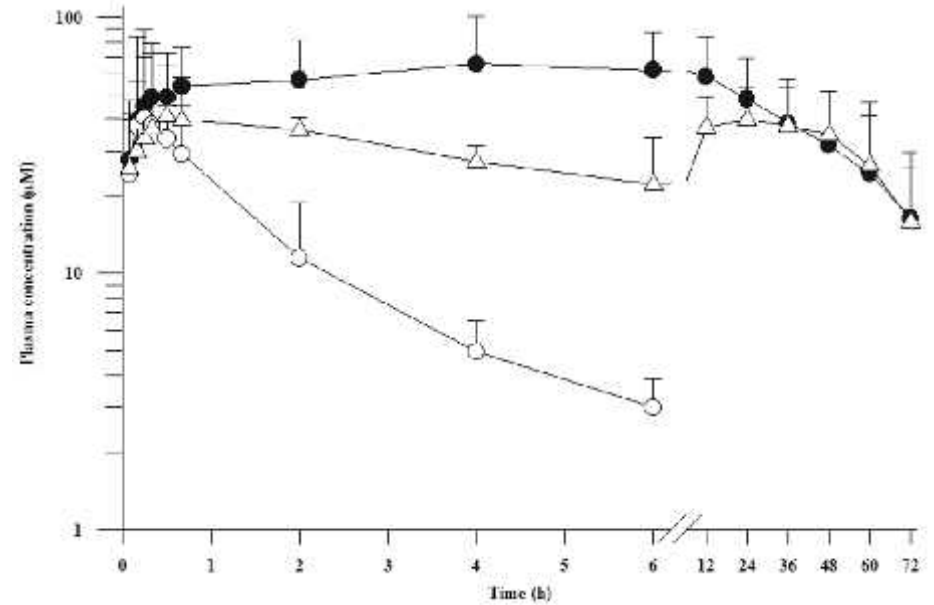


Phenytoin and Fosphenytoin

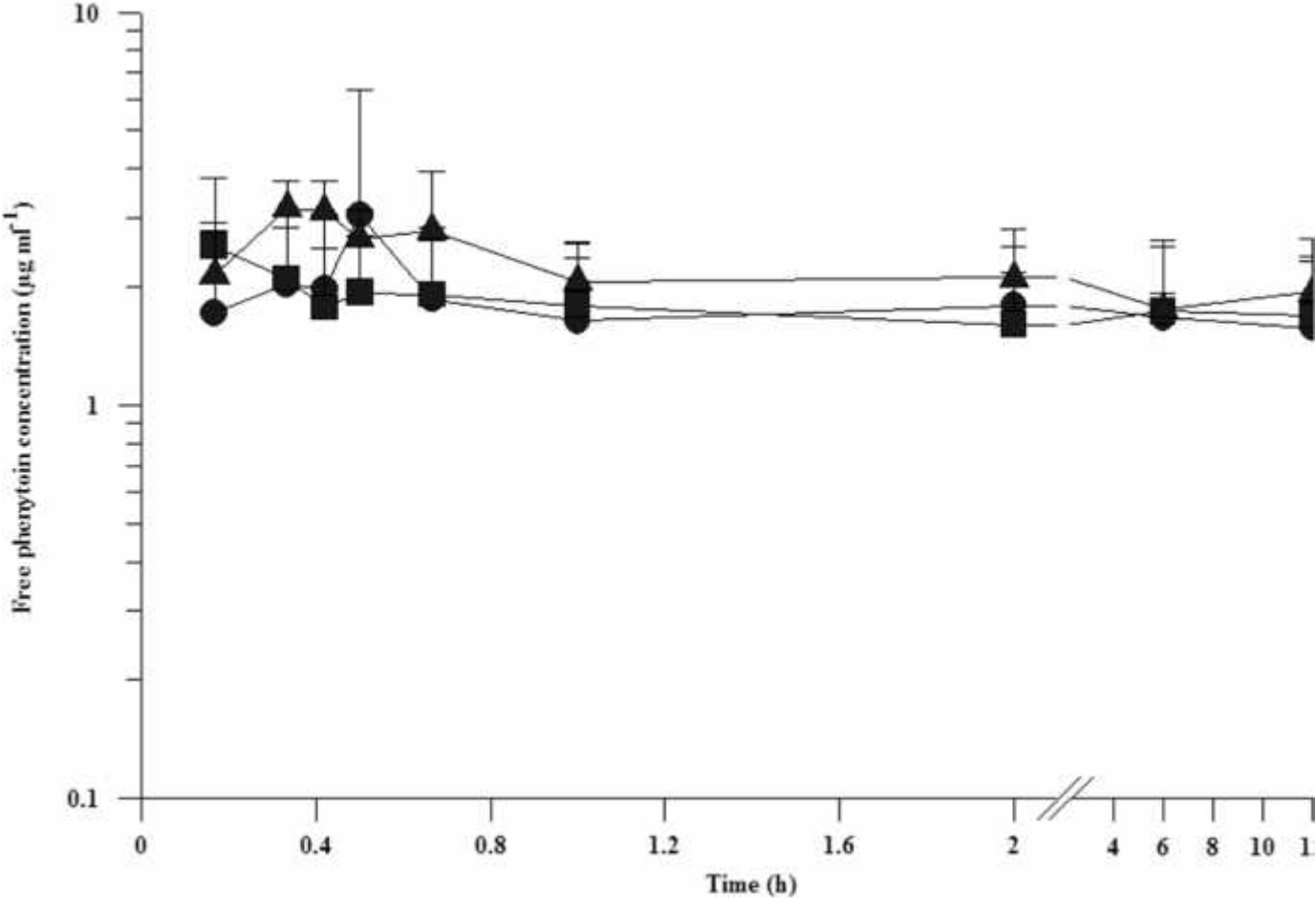
Cefotaxime



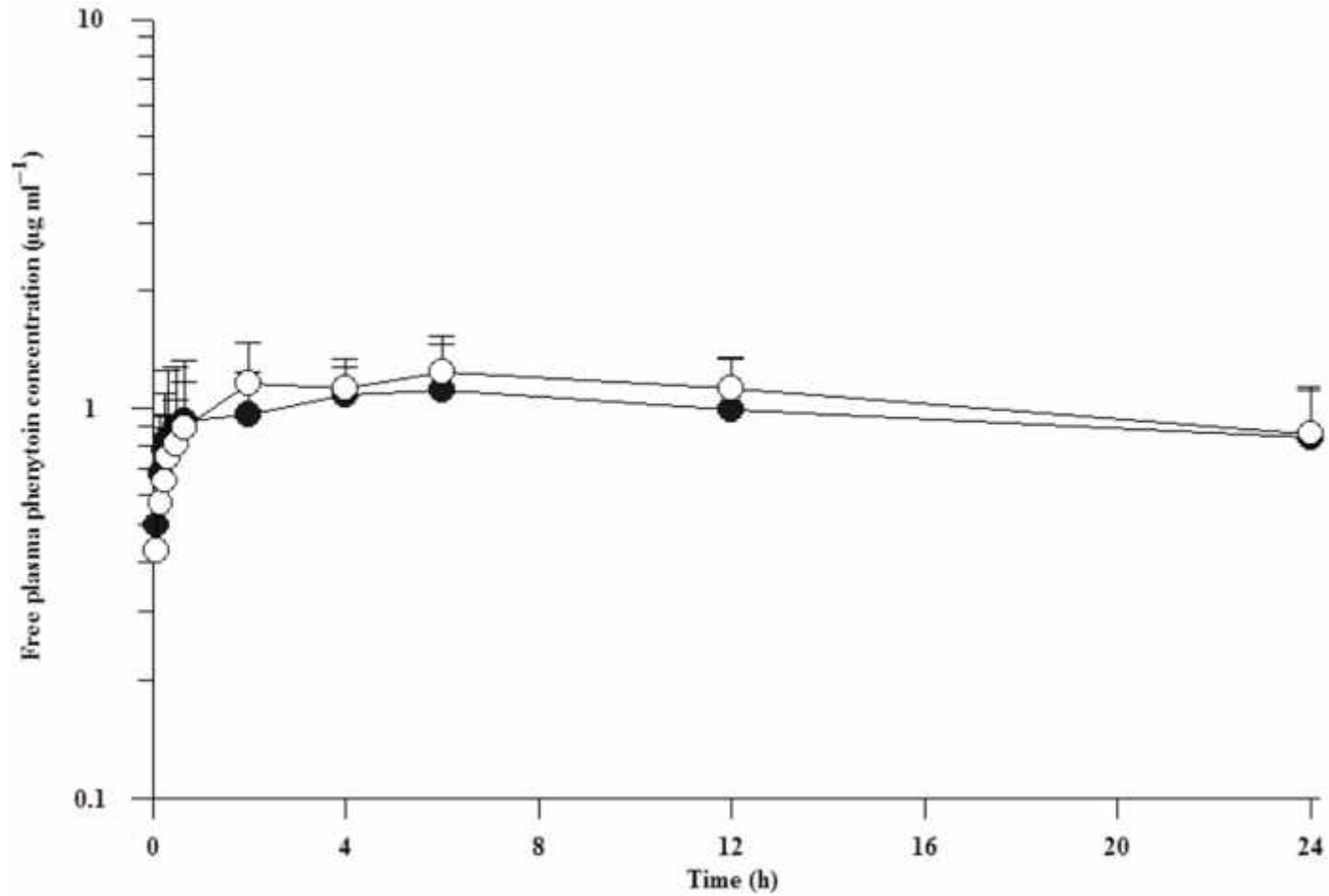
Chlramphenicol



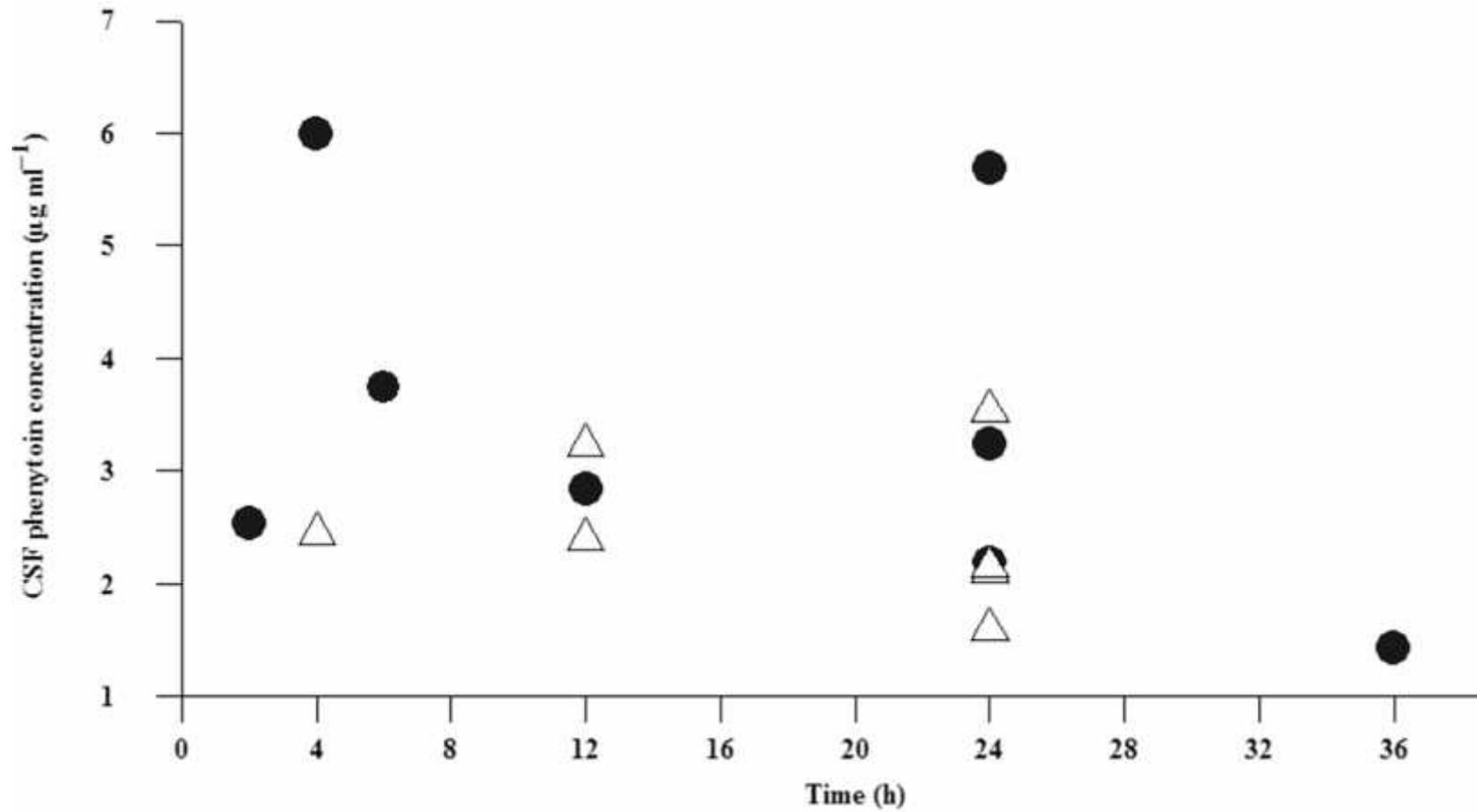
Mean free plasma phenytoin concentrations following IV phenytoin (triangles), and fosphenytoin IV (squares) and IM (circles).



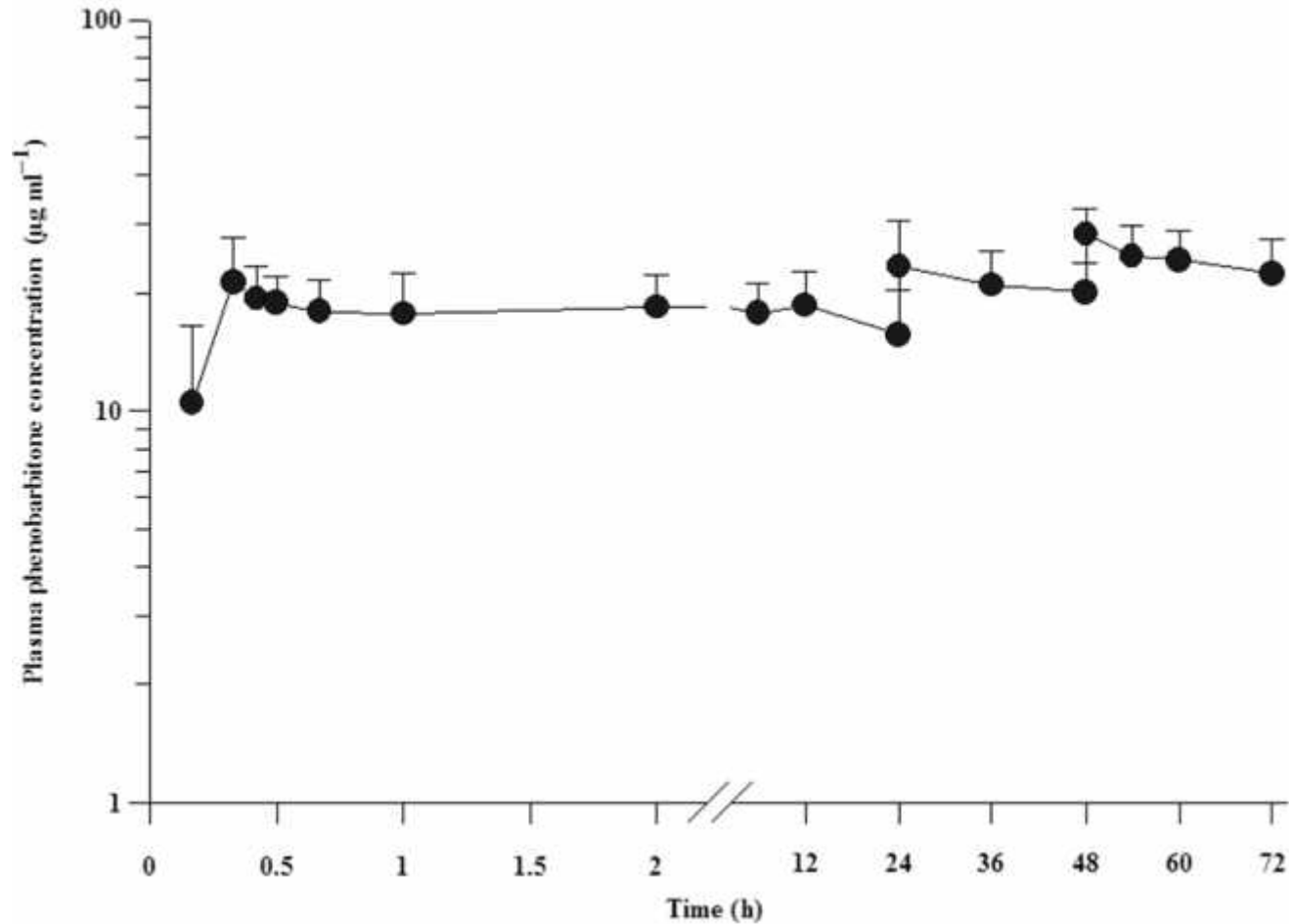
Free plasma concentrations of Phenytoin(chlram/Cefo)



CSF conc.(chlram/Cefo)



Mean plasma phenobarbitone concentrations following IV administration (loading 15mg/5mg)



What Next

- Therapeutic drug Monitoring
- Understanding Kenyan pharmacogenomics
- Identifying the pharmacological islands in paediatrics