Children are small adults and babies are young children

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Objectives

- Appreciate how clinical pharmacology has helped medical practice
- Review examples of real research projects
- Recognize the challenges of getting doctors to use science in their daily practice

Clinical pharmacology describes the effects of drugs in humans. One way to think about the scope of clinical pharmacology is to understand the factors linking dose to effect. Drug concentration is not as easily observable as doses and effects. It is believed to be the linking factor that explains the time course of effects after a drug dose.

The science linking dose and concentration is pharmacokinetics. The two main pharmacokinetic properties of a drug are clearance (CL) and volume of distribution (V).

The science linking concentration and effect is pharmacodynamics. The two main pharmacodynamic properties of a drug are the maximum effect (Emax) and the concentration producing 50% of the maximum effect (C50).
A study of the effects of theophylline in patients with severe airways obstruction was carried out at Auckland Hospital. It showed that the target concentration is 10 mg/L. Higher concentrations had little extra benefit but substantially more toxicity e.g. nausea and vomiting.

The primary objective of this study was to determine which target concentration was safe and effective when starting treatment with theophylline.

**What Was The Clinical problem?**

- Severe asthma and COPD are very common causes of hospital admission.
- Intravenous theophylline was the standard emergency treatment.
- But what was the right starting dose?
- The target concentration approach was being discussed by clinical pharmacologists but 'real doctors' had no idea what it was about.

**Target Concentration Controlled Clinical Trial**

- Patients were randomized to a target conc of 10 or 20 mg/L.
- Laboratory scaled the actual measurements e.g. if the target was 10 mg/L and the actual conc was 10 mg/L, it was reported as 15 mg/L.
- Only the lab knew the actual value. Scaled values were reported to doctors. This maintained the double blind feature of the trial.
- Doctors used the reported theophylline concentrations to try to target 15 mg/L by changing IV infusion rate.

COPD = Chronic Obstructive Pulmonary Disease

Theophylline is administered using an intravenous formulation of aminophylline which contains 80% theophylline by weight.
The Outcome of the Trial

- Trial showed 10 mg/L was safer than 20 mg/L
  - 20 mg/L group included vomiting, arrhythmias and convulsions
  - Little difference in effects on peak expiratory flow rate
- Conclusion: Target concentration is 10 mg/L
- Doctors had a clear idea of how to start and adjust doses for individualized safe and effective treatment
- Research example for clinical pharmacologists (Sheiner 1997)

**CLINICAL PHARMACOLOGY & THERAPEUTICS**

**COMMENTS**
Learning versus confirming in clinical drug development

Nick Holford (left) and Brian Anderson (right) at Seoul Hilton, Korea, 2012

Professor Sheiner is probably the most important figure in the development of rational clinical pharmacology – especially for bringing a quantitative approach to decisions about the development and clinical use of medicines. He trained many clinical pharmacologists who use his ideas every day in clinical practice, research and teaching e.g. Professor Park (Seoul, Korea), Professor Karlsson (Uppsala, Sweden), Professor Holford (Auckland, New Zealand)
Paediatric Clinical Research

- Brian Anderson, consultant intensive care physician at StarShip Hospital, Auckland, New Zealand
  - Mid-life crisis so decided to do a PhD
- Studies of pharmacokinetics and pharmacodynamics of paracetamol in children after tonsillectomy
- Pharmacodynamic study used doses of 100 mg/kg compared to traditional doses of 40 mg/kg by the rectal route to establish the maximum pain relief (Emax) and potency (C50)

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How Does Paracetamol Work?

- POX site of Prostaglandin H2 synthetase (PGHS) enzyme
- Metabolite (N-arachidonoylphenolamine, AM404) is endogenous cannabinoid
- CB(1) receptor antagonist completely prevents the analgesic activity of paracetamol

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Tonsillectomy Pain Resolution

**Paracetamol Pharmacodynamics**

Note large placebo response (difference between predicted paracetamol effect (acetaminophen PD prediction)) and pain score with different doses and routes.

**Paracetamol Analgesia and Toxicity**

- 5 mg/L  1.7 pain units
- 10 mg/L  2.6 pain units
- 20 mg/L  3.4 pain units
- 30 mg/L  4.2 pain units

- Paracetamol 100 mg/kg  11/20 vomited
- Paracetamol 40 mg/kg  3/12 vomited

- Vomiting more frequent with high dose (Chi square, p=0.037)
- Vomiting with high dose similar to morphine

**Paracetamol Target Concentration**

- Recommended target concentration is 10 mg/L
- This concentration affords reasonable analgesia
- The target concentration is easily achieved in most individuals using the recommended dosage schedule.
- While higher doses could achieve greater analgesia, chronic use of higher doses is associated with an increased incidence of hepatotoxicity.
  - Note: The adverse effects on the liver short term use of higher doses e.g. for a target of 20 mg/L, are unknown.
  - To be safe: “First do not harm”/“Primum non nocere”

**Pharmacokinetic Model for Children**

- Results from the pain relief study were combined with other studies in children and adults.
- Pharmacokinetic model showed how concentration depends on size (weight) and maturation (age).
  
  » Anderson et al. 2000, Anderson & Holford 2011

**Application of PK to Clinical Practice**

- Paracetamol accidental overdose is common in infants and children.
- Guidelines for treatment in adults starts by measuring paracetamol concentration at 4 hours after ingestion.
  
  » 4 hours is a long time to wait for children (and adults!)
- Auckland pharmacokinetic model was used to simulate concentrations after overdose with liquid ("elixir") formulations usually taken by children.

**Accidental Ingestion in Children Recommendations**

- Measure concentration if ingestion > 200 mg/kg of elixir (or if dose unknown)
- Obtain sample at two hours
- If 2 h level is > 150 mg/L, then a second level should be measured at 4 hours
- Start N-acetyl-cysteine if plasma conc. > 150 mg/L (4 h)


The paracetamol model was updated again in 2011:


International Recognition


Blood sample at 2 hours after ingestion
Less stress; shorter time in hospital

International Collaborations

- Paracetamol work led to fame in the paediatric world
- Invited to work on data collected by other groups who were impressed by our PKPD approach
- Morphine, Ketamine, Clonidine, Dexmedetomidine, Tramadol…

Morphine

- Dutch group – infants and children
- American group – premature neonates
- PK model
  - Allometric size
  - Maturation based on post-menstrual age
- Predictions compared to literature values from neonates to elderly
  - Theory based allometry and maturation was the only method that predicted acceptable doses across human age range

General Principles Learned from Paracetamol Studies in Children

Clearance Maturation

Maturation is complete by 2 years of age – then weight is the sole predictive factor for drug clearance.

Post-menstrual age is the recommended way to describe the biological age in weeks after conception. It is based on the mother’s recall of the date of the last menstrual period. It is therefore typically biased by overestimating the age since conception by 2 weeks.

Clearance increases with weight and age (red line). Allometric size predicts increasing clearance per kg with lower weights (green line). Below 2 years of age immaturity of drug clearance has a major effect on clearance (see inset) so clearance per kg decreases. This leads to a peak in clearance when expressed per kg around 2 years of age. Clinically used maintenance doses are commonly expressed per kg in clinical practice and are higher around 2 years of age than in babies and adults.
Weight is combined with post-natal age (PNA) and post-menstrual age (PMA) to predict the typical dose as a % of the adult dose. The coloured areas of the table show the fraction of adult maintenance dose that would be expected for infants and children. The fractions are based on the theoretical size and maturation model for typical drug clearance with some approximation to make the numbers easier to remember. The ‘rule of PMA+PNA’ has an acceptable error for clinical dose prediction. Although maturation is best described by a non-linear relationship it is quite well approximated by a linear function of PMA.


A High Clinical Need

- Busulfan is used to knock-out bone marrow in children and adults prior to bone marrow transplant
- High mortality (30%) due to drug toxicity or graft failure
- FDA product label recommends using AUC to individualize subsequent doses
- Auckland Hospital asks “How to calculate AUC for busulfan?”

AUC Dose Adjustment from Busulfex label (PDL 2006)

Calculation of AUC:

\[
\text{AUC} = \text{Dose} \times \text{t} \times \text{AUC}
\]

Busulfan Collaboration

- American national lab for measuring busulfan asks for assistance in PK analysis of concs from 1610 patients
- Allometric size, maturation and normal fat mass used to predict initial doses
- Initial dose predictions much better than FDA method (72% vs 57% acceptable)
- But still 28% with unacceptable dose …
Why Target Concentration Intervention is Necessary

- The acceptable exposure range for busulfan is based on a goal of 95% of patients lying within 80-125% of the target average steady state concentration (Css) (Holford & Buclin 2012)

- With TCI the unpredictable variability for Css can be reduced to the within subject variability of 11.3% (McCune 2014)

- This means that only 5% of patients will be under- or over-dosed if measured concentrations are used to predict future doses. A major improvement over initial dosing based on size and age.


Way to go!