Session 6 - Innovative designs, pharmacometrics and optimal designs

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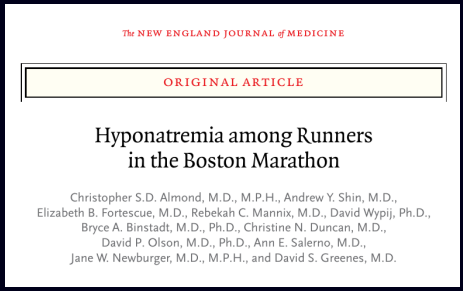
What “Biological priors” do we have on the system that will generate our data?

Standing JF BJCP 2017

Biological Priors since 1493

What is the dose-concentration-effect relationship? How does it evolve with time?

"Poison is in everything, and no thing is without poison. The dosage makes it either a poison or a remedy."



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Hyponatremia among Runners in the Boston Marathon

Christopher S.D. Almond, M.D., M.P.H., Andrew Y. Shin, M.D., Elizabeth B. Fortescue, M.D., Rebekah C. Mannix, M.D., David Wypij, Ph.D., Bryce A. Binstadt, M.D., Ph.D., Christine N. Duncan, M.D., David P. Olson, M.D., Ph.D., Ann E. Salerno, M.D., Jane W. Newburger, M.D., M.P.H., and David S. Greenes, M.D.

Biological priors: pharmacokinetics

Recall the 1-compartment iv bolus model:

$$C(t) = C(0)e^{-kt}, \tag{1}$$

where $C(t)$ is the concentration at time t, $C(0)$ is the initial concentration given by D/V, and k is the elimination rate constant related to V via $k = CL/V$.

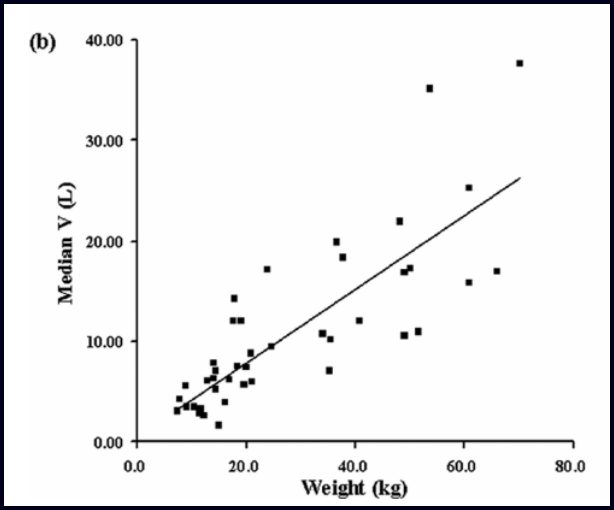
V, CL (and k) are **parameters**, the values of which are estimated from **observations** $C(t)$ and **covariates** D and t

1. Which PK parameter do we need to estimate C_{max}?
2. Which PK parameter do we need to estimate AUC?
3. Which PK parameter do we need to estimate $t_{1/2}$?

How do V, CL and $t_{1/2}$ vary with size and age?

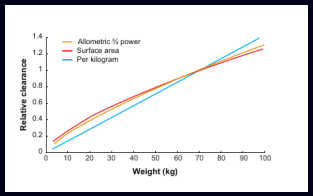
Volume of distribution (V)

Usually linear with weight, e.g. Zeng 2009

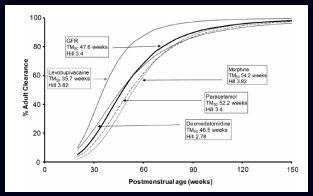


Clearance (CL), Crawford 1950 Pediatrics

BIOLOGICAL PRIOR:
Liver volume $\propto wt^{0.78}$ (Johnson 2005)
Glomerular filtration $\propto wt^{0.63}$ (Rhodin 2008)



Maturation:



PK OBSERVATION:

Small molecules (Burger 2007):

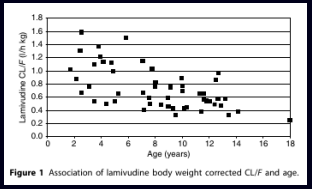
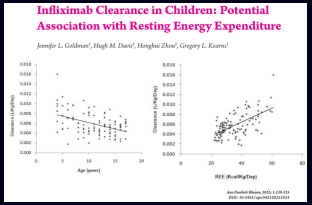


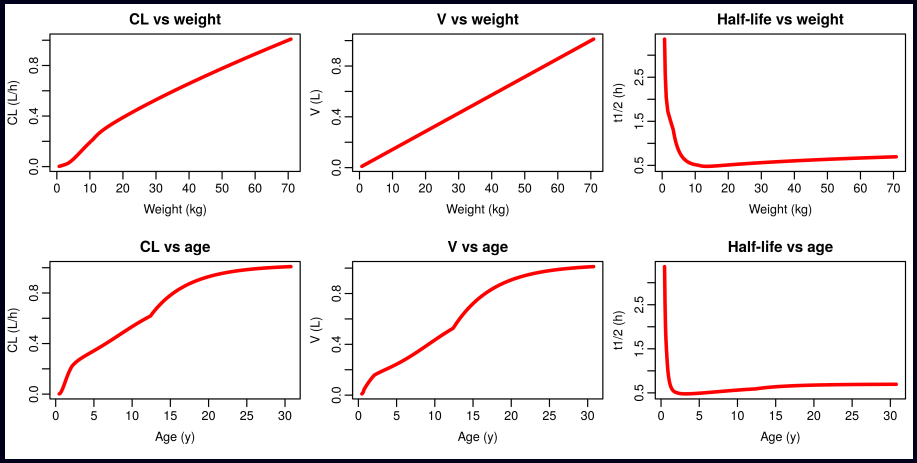
Figure 1 Association of lamivudine body weight corrected CL/F and age.

Biologics (Goldman 2012):



Ontogeny of CL, V, $t_{1/2}$

- For equivalent C_{max} dose mg/kg
- For equivalent AUC dose mg/m^2 and reduce in neonates/infants
- For equivalent C_{min} might need higher doses in young children (are you sure your target is C_{min}



Biological priors: Pharmacodynamics, AV Hill, born 1886

Law of mass action: Drug (D) combining with Receptor (R)

$$[D] + [R] \rightleftarrows [DR], \tag{2}$$

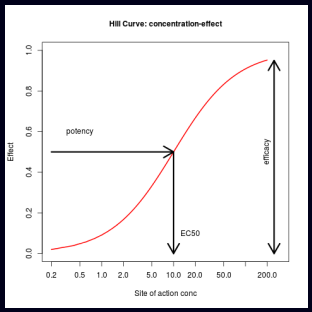
$$[DR]k_{off} = [D][R]k_{on}. \tag{3}$$

Assume finite receptor capacity

$$[R_{tot}] = [R] + [DR]. \tag{4}$$

Remove dependence of $[DR]$ on $[R]$, assume $Effect \propto [DR]$, and can show $EC_{50} = \frac{k_{off}}{k_{on}}$

$$Effect = E_{max}\frac{C^{\gamma}}{EC50^{\gamma} + C^{\gamma}}. \tag{5}$$



What does dose-response look like?

Meta-analyses of clinical dose response, 11 year period of Pfizer data presented at EMA D-E-R workshop in 2014: N. Thomas D. Roy, V. Somayaji, and K. Sweeney

Summary

What do clinical dose response curves look like?

Most look like hyperbolic $\mathrm{E}_{\mathrm{max}}$ curves.

Conclusion:

- We know the model and (lose efficiency using a different one, Mentre?)
- Will need a big (10-fold if $\gamma = 1$) dose range to properly characterise - will this be possible in "small" populations?
- Focus on how/whether PD may scale e.g.:
  - 1 year old has 3-fold higher CD4 count than 5 year old - PD scaling applied in RL Hoare et al 2017 CPT
  - Adolescents have 4-fold higher IGF-1 level than 1 year old (drops again in adulthood) see A Rao et al 2013 BMJ Open

Discussion from session 6

Session 6 discussion:

Pharmacometric NLME designs

- Framework to incorporate biological priors
- RCT on pharmacometric model parameter for power gain:
  - Lots of nice simulation examples, must be plenty of real clinical trial data to retrospectively explore before someone dares run a prospective trial?

Adaptive design:

- Need for/feasibility of "on-call" stats/PMx input?
- Rule based designs prevail but inefficient (Wheeler 2016)

Session 6 discussion:

Cross-over and N-of-1:

- Delayed toxicity not attributed when patients all exposed to both treatments
- Similarly need rapid PD measure (how many chronic diseases have this?)

Historical controls:

- Treat with caution if at all
- Finalising data analysis plan pre-trial - can pharmacometrics learn to do this?

Improving MTD

- Is MTD relevant outside (old style) oncology drugs? Can we extend to efficacy?
- Dose ranging important with uncertainty in PD