Quantitative Pharmacology

Where have we been?
Where are we going?

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Conception
Medical Student + Guinea Pig Ileum

"Dilution Error" – this is why I don't do lab work!

Birth

• Hill
  – Quantitative receptor theory (+ empiricism)

• Arunlakshana & Schild
  – Competitive interaction

Childhood

- Holford & Sheiner
  - Understanding the concentration-effect relationship

- Stanski, Weiss, Levy
  - Delayed drug effects
  - Distribution, binding, turnover

Teenage Girl meets Boy
Variable PK meets PD

- Sheiner & Beal 1978
  - The population approach

- Tanigawara 1997
  - Bridging with the world

Origin of Pharmacometrics

Evaluation of Drug Activities: Pharmacometrics

The new term, and new journal section, is meant to focus on the metric (measurement) concerns peculiar to the readership of JPB: the design, modeling, and analysis of experiments involving complex dynamic systems in the field of pharmacokinetics and biopharmaceutics.

Maturation

- Tools
  - NONLIN -> WinNonLin
  - NONMEM -> NM-TRAN
  - Clinical Trial Simulator

- Communities
  - nmusers and pharmpk
  - PAGE, PAGANZ, PAGJA, PAGK, PAGIN, ACoP, WCoP
  - ISoP

Adult Topics

- What are the lessons we still have not learned properly?

- What are the important factors determining dose?

- How can PKPD help drug development?

- How can pharmacometrics help patients?

Encouraging better use of drug concentration measurements in the laboratory

- Chemical analysts continue to report measured concentrations as being below the limit of quantitation (BLQ) when the value is less than the lower limit of quantitation.

- Providing BLQ values rather than the actual measurement causes bias in the estimation of pharmacokinetic parameters and may lead to selection of an inappropriate model.

- Chemical analysts should be encouraged to help pharmacokinetic analyses by reporting what they measure and not censor the data by inappropriate application of guidelines for validation of assay methodologies.
We don’t need this if chemical analysts are honest

"If the times of the BQL observations are not available, then adjusting the likelihoods for the remaining data (M2) may improve parameter estimates compared to no adjustment (M1)."

"In most cases, the time when the BQL observations occur are recorded and a better approach for handling BQL data would be treating them as censored observation (M3)."


Understanding that Area under Curve, Tmax and Cmax are not pharmacokinetic parameters

• Naïve descriptions of the time course of drug concentration are reported in terms of area under the curve, peak measured concentration and time to peak concentration.

• These are pharmacokinetic statistics but they are not pharmacokinetic parameters.

• They are not parameters because they depend on the dose and on the design of the study.

Time for ADME to be Forgotten

Pharmacokinetic Models (IDO)

Pharmacokinetics is a science that studies the key processes of input, distribution and output of drugs from living organisms. Input processes describe controlled administration (e.g. IV infusion) and absorption from a depot (e.g. oral dosing). Output includes metabolism to another molecule (e.g. by cytochrome enzymes) and excretion as unchanged molecule (e.g. in the urine).

Older descriptions of PK refer to ADME (absorption, distribution, metabolism, excretion) but this 4 component classification does not properly include drug input that is not absorption and unnecessarily splits output into metabolism and excretion. Pharmacokinetic models are created by combining models for input, distribution and output (IDO).

http://www.mashframe.com/isop_wiki
**Body size** is the most important quantitative determinant of drug dose

- The human body weight range varies from about 500 g to over 250 kg due to both biological variability and changes over the lifespan.

- This more than 500 fold range in size is directly translatable through volume of distribution into drug **loading dose** differences.

- Because of allometrically predictable relationships between weight and clearance the corresponding range of **maintenance dose rates** is only about 100 fold.

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Theoretical Foundation for Allometric Scaling


\[
\frac{CL_{\text{ADULT}}}{CL_{\text{CHILD}}} = \left(\frac{WT_{\text{ADULT}}}{WT_{\text{CHILD}}}\right)^{4/3}
\]

The fundamental assumption of West’s allometric theory is that all cells are similar in size and have similar energy requirements. The structure of the energy delivery system e.g. blood vessels in humans, requires a certain mass to support the delivery system as well as the target cells. This leads to the theoretical allometric scaling function with a power of \(4/3\).

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Estimation of Allometric Exponent

<table>
<thead>
<tr>
<th>Weight distribution</th>
<th>90% CI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log normal median 74 kg, 10% CV</td>
<td>0.69</td>
<td>1.01</td>
</tr>
<tr>
<td>Log normal median 74 kg, 15% CV</td>
<td>0.64</td>
<td>0.86</td>
</tr>
<tr>
<td>Uniforms 0-240 kg</td>
<td>0.69</td>
<td>0.81</td>
</tr>
</tbody>
</table>

Don’t do it unless you know you can account for all other size associated factors and have the right distribution of weights!
**Standard Weight for Allometric Models**

Concern is expressed sometimes that scaling parameter values estimated in neonates and children in terms of an adult size standard of 70 kg may bias the estimates or affect the precision of estimation. There is no basis for this concern. This can be seen by inspection of the allometric covariate model which may be re-arranged:

\[ F_{size} = (W)^{1/4} \cdot \left( \frac{V}{70} \right)^{1/4} \]

The expression

\[ \left( \frac{V}{70} \right)^{1/4} \]

is simply a constant that is determined by whatever weight is chosen for standardization. The precision of a parameter estimate will not be changed by multiplying the parameter value by an ad hoc constant.

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**Renal function and post-menstrual age are the next most important determinants of drug dose**

- Differences in renal function can explain about a 10 fold difference in total drug clearance. In neonates and infants age accounts for a 10 fold increase in glomerular filtration rate from 24 weeks post-menstrual age up to 1 year of post-natal age (Rhodin, Anderson et al. 2009).

- Maturational changes of 10 fold have been observed for drug clearances. Age in older adults has a minor influence on drug clearance (once weight and other factors such as renal function are accounted for).

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**Clearance Maturation**

Maturation is complete by 2 years of age – then weight is the sole predictive factor for drug clearance.
Body size, renal function and post-menstrual age are the most important determinants of drug dose

- In comparison to these factors other covariates such as genotype often pale into insignificance.
- Quantitative pharmacology can help put the role of using covariates to predict drug dose into a realistic perspective.

Drug Development - Linking PKPD and disease progress to clinical outcome

- PKPD models are usually based on biomarkers that are not directly connected to patient symptoms or improvement in function or survival.
- It is only recently that methodology has been developed and applied to biomarker based PKPD which can be used to understand and predict clinical outcome.
- These quantitative links between the time course of biomarkers and the time to a clinical event represent the next step forward for understanding and predicting clinical pharmacology.

PKPD Predicts Outcome

Making the most of drug concentration measurements at the bedside

- Measurements of drug response after starting treatment e.g. international normalized ratio or drug concentrations, have long been held out as a method for **dose individualization that goes beyond the use of covariates** such as weight, renal function and age.

- Therapeutic drug monitoring is involved with measurement of drug concentrations but the link between the measurement and individualization of dose **requires more than just comparing the concentration to a therapeutic range**.

Making the most of drug concentration bedside

- Despite a **clear demonstration of improved survival** in acute lymphoblastic leukemia when methotrexate doses are based on **Bayesian predictions of clearance**, this breakthrough in treatment of the disease is still rarely used because of the perceived **difficulties of interpretation of the concentrations**.

- The widespread availability of access to **computational resources on the internet** opens up the possibility of making Bayesian methodologies available at the bedside to any clinician with a smartphone.


The Birth of Clinical Pharmacometrics


**Computer-Aided Long-Term Anticoagulation Therapy**

**Lewin B. Shenker**

*Division of Computer Research and Technology, National Institutes of Health, Public Health Service, Department of Health, Education, and Welfare, Bethesda, Maryland 20014*

\[
\frac{dC}{dt} = -k_1 C F + (1 - aD) C(0), \quad \text{for } 1 - aD > 0, F < 1 \\
\frac{dD}{dt} = -k_2 D F, \quad \text{for } 1 - aD < 0 \text{ or whenever } F = 1,
\]

where \( F \) is the "clearing factor" level, \( \frac{dC}{dt} \) is the rate of change of \( C \) with time, \( k_1(2) \) is the rate constant for the decay of \( F \), \( D \) is the drug level (substitute the equation for \( D \), above), \( k(3) \) is the normal maximal synthesis rate of the clotting factor and \( a \) is a "sensitivity factor" relating a given drug level to its effect on synthesis.
Clinical Pharmacometrics Today

An Introduction to NextDose

What is it and why should you use it?

Bayesian Forecasting

Cross-pollination using Bayesian forecasting has been shown to save lives. Dose et al. demonstrated a larger increase in survival for individualised vs. conventional dosing, by individualising neoadjuvant dose, than any other single drug treatment (Dose, Rolling et al. 2001). Despite its intriguing improvement in 3-year survival, it is largely used because of the difficulties of access to, and usability of, Bayesian forecasting software. Dose individualisation has also been shown to increase survival after disease recurrence (by maintaining target within a narrow therapeutic range (Dose et al. 2001, Skibber, Ziegler et al. 2001, Gridley, Rutman et al. 2007). Scandvik, Bendas et al. 2009, Akinsin, Vidmar et al. 2010). In addition to the oncological applications, data is an integral part of clinical staff search tool to help make the best use of scarce resources. NextDose was developed to extend this tool and promote ongoing collaboration in biomarkers, with data sharing in NHMRC.


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What Next?

http://www.go-isop.org

• JOIN
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• EXPLORE
• DONATE