Nomogram to NextDose
Body Size, Maturation and Organ Function

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My first job as a medical doctor was a House Surgeon at Macclesfield Hospital in 1972. I only did minor surgery but I won acclaim from my surgical colleagues for predicting doses of gentamicin using George Mawer’s nomogram. The nomogram uses weight, age, sex and serum creatinine for loading and maintenance doses. Dosing was always 8 hourly. I carried paper copies of the nomogram with me in my pocket and could quickly recommend a dose in patients needing gentamicin for treating surgical infections. There were no measurements of gentamicin available at that time so there was no question of further individualization.

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

Shortly before I took up my first medical job in 1972 I was examined orally for and won a prize for medicine. One of the exam questions was how to individualize the use of azathioprine (a question asked by a neurologist). I figured out the answer was to use weight and prescribe a mg/kg dose. At the time that was considered highly sophisticated.

Today we can recognize that weight is the most important single covariate for dose individualisation in humans. Weight explains at least a 100 fold difference in dose in order to maintain a target concentration.
Theoretical Foundation for Allometric Scaling

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 e.g. bones in humans, to support the delivery system as well as the target cells. The mass overhead from these delivery and support systems increases total body mass without a linear increase in function. The allometric exponent value of \( \frac{3}{4} \) describes this non-linear relationship for clearance. This concept is true for both animals (e.g. humans or elephants) and plants (e.g. sequoia or kauri).

In contrast to functional processes such as clearance, allometric theory predicts a linear relationship between mass and structural properties such as volume of distribution. The allometric exponent for volume of distribution is 1.

Photo shows Nick Holford (41 y 80 kg) and Sam Holford (1 y 8 kg) on Fox Glacier, NZ 1987

Renal Function

- Differences in renal function can explain about a 10 fold difference in total drug clearance.
- Glomerular Filtration Rate
  - 7 L/h in healthy young adult
  - 0.5 L/h in terminal renal failure
- There is always some non-renal clearance e.g. via the gut which adds 0.5 L/h to renal clearance even in renal failure

Renal function based on GFR are important but still less than weight after accounting for body size.
Hepatic Function

- Difficult to predict hepatic drug clearance without administering the drug
- "Liver Function Tests"
  - measure liver damage which is not the same as function
- Clinical Staging Systems
  - Childs Pugh system/MELD/HPSE
  - Loosely correlated with hepatic drug clearance

There is a very important biological difference between age in young humans and old humans. Young humans (babies, infants) are immature. They have size appropriate organs but have not yet developed functional capacity. Old humans lose renal function as a consequence of nephron loss related to environmental hazards (not age) but do not lose hepatic function because the liver regenerates its cells and enzymes irrespective of age.


Population predictions of hepatic function are possible but individual predictions do not have any reliable biomarkers like serum creatinine for renal function.

MELD=Model for Evaluation of Liver Disease
HPSE=Hepatic Portal Systemic Elements

Maturation and Ageing

- Maturation Of Drug Clearance
  - Typical maturation is about 30% of adult values at full term delivery
  - Very premature neonates are around 10% of adult values
  - 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 et al. 2009).

- Ageing and Drug Clearance
  - Age in older adults has a minor (~ 25% lower) influence on drug clearance once weight and other factors such as renal function are accounted for.

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. Maintenance doses are commonly expressed per kg in clinical practice and are also higher around 2 years of age than in babies and adults. The green line (clearance/kg) is consistent with long standing empirical knowledge of drug dosing in children. It is explained by the combination of two biological processes – size and maturation.
NextDose was developed in collaboration with my son, Sam Holford (see Slide 4). He created the web interface to the modelling backend that I worked on. Sam is now a practicing medical doctor. We continue to work on developing NextDose.

Technology

- Software abstraction layers
  - NONMEM core
    - NMTRAN input
    - Bayesian methodology
  - awk pre & post processor
    - Dose proposal
    - Concentration predictions
- PHP + MySQL middleware
  - User + clinical record keeping
  - Translation to/from Awk
- HTML5 + JavaScript UI

A collaborative effort

Clinicians
- age
- weight
- disease

Pharmacists
- formulation
- dose
- time

Phlebotomists & nurses
- blood sample time

Laboratory
- concentration determination

Common interface for use at different times and locations for all involved
Opportunities
- Voriconazole
- Aminoglycosides
- Other medicines

Challenges
- Motivation
  - Clinical staff
  - Management
- Record keeping
  - Audit trail
  - Authorisation
- Browser compatibility
- Security
  - Software
  - Privacy
  - Location
  - Reliability
- Software errors
  - Catching them
  - Prevention
  - Setting expectations
- Support
  - Staffing
  - Back up methods

Browser compatibility

Conclusion

- Nomograms or NextDose?
  » https://dev.nextdose.org/
- Interesting intellectual challenges
  » Scientifically rewarding
- Clinical pharmacology is fun!
Rules of PNA and PMA
Fraction of adult maintenance dose

<table>
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<tr>
<th>Typical Weight Kg</th>
<th>PMA or PNA</th>
<th>Fraction Adult Dose</th>
<th>Rule of PMA+PNA Error</th>
<th>'true' % Adult Dose</th>
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<td>25 weeks</td>
<td>1/300</td>
<td>10%</td>
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<tr>
<td>1</td>
<td>30 weeks</td>
<td>1/120</td>
<td>1%</td>
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<td>3</td>
<td>Full Term</td>
<td>1/30</td>
<td>1%</td>
<td>3.3</td>
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<tr>
<td>6</td>
<td>3 mo</td>
<td>1/10</td>
<td>8%</td>
<td>9.3</td>
</tr>
<tr>
<td>7</td>
<td>6 mo</td>
<td>1/6</td>
<td>24%</td>
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<td>1 year</td>
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<td>3%</td>
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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.