Objectives

1) Appreciate how a target concentration (TC) strategy is essential for rational drug development and clinical use
2) Distinguish target concentration intervention (TCI) from therapeutic drug monitoring (TDM)
3) Understand why safe and effective variability (SEV) has to be defined in order to make rational choices for dose individualization
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 (EC50).

Effective drug development needs a plan
- A good plan has a clear objective
- TC provides a clear objective in all phases of drug development

TC is the rational basis for dose individualization
- Choose the target effect to determine the TC
- Use TC to predict individual dose

The 1992 view was based on using PKPD for drug development but did not explicitly include how to use medicines in patients.
Target Concentration in Clinical Use of Medicines

Ideal dose prediction requires individual estimates of Emax, EC50, V and CL

**Dose Model**
- **Initial Peak**
  - Loading Dose = \( \text{Target Conc} \times \text{Volume of Distribution} \)
- **Average Steady State**
  - Maintenance Dose Rate = \( \text{Target Conc} \times \text{Clearance} \)

The target concentration approach links PKPD to prediction of the right dose for a patient.

**TDM or TCI?**
- **Therapeutic Drug Monitoring**
  - TDM Therapeutic Range
    - Toxic
    - Imprecise
    - Sub-optimal at borders of the range
  - TCI Single Target
    - Accurate
    - Ideal
    - Optimal – do the best you can

**How to Find the Target?**


Theophylline Target Concentration in Severe Airways Obstruction – 10 or 20 mg/L?
A Randomized Concentration-Controlled Trial

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- Randomized concentration controlled trials are the gold standard
Why does PKPD vary?

- **Systematic (predictable)**
  - Body size
  - Disease state (liver, kidney)
  - Genotype
  - etc...

- **Random (not predictable)**
  - Between Subject Variability
  - Within Subject Variability

Predictable Variability
Size and Maturation


- ¾ Allometry Alone explains 67% of CL variability
- ¾ Allometry + Maturation explains 80% of CL variability

Toddlers under-predicted
Neonates over-predicted

Covariates Do Not Explain All Variability

Clearance

Artefact from per kg scaling!

N.Sambol CDDS/SUMC1997
Unexplained Clearance Variability

<table>
<thead>
<tr>
<th>Drug</th>
<th>BSV %</th>
<th>WSV %</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metoprolol</td>
<td>53</td>
<td>35</td>
<td>Lunn (1997)</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>12</td>
<td>16</td>
<td>Bouillon (1996)</td>
</tr>
<tr>
<td>Rituzole</td>
<td>51</td>
<td>28</td>
<td>Bruno (1997)</td>
</tr>
<tr>
<td>Felodipine</td>
<td>34</td>
<td>33</td>
<td>Wade (1995)</td>
</tr>
<tr>
<td>Drug A</td>
<td>57</td>
<td>29</td>
<td>Karlsson (1993)</td>
</tr>
<tr>
<td>Drug B</td>
<td>35</td>
<td>19</td>
<td>Karlsson (1993)</td>
</tr>
<tr>
<td>Drug B</td>
<td>33</td>
<td>19</td>
<td>Jonsson (1996)</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>22</td>
<td>15</td>
<td>Karlsson (1999)</td>
</tr>
<tr>
<td>Artemisinin</td>
<td>48</td>
<td>53</td>
<td>Siddhu (1998)</td>
</tr>
<tr>
<td>Average</td>
<td>41</td>
<td>30</td>
<td></td>
</tr>
</tbody>
</table>

BSV = Between Subject
WSV = Within Subject

Safe and Effective Variability

- CLINICAL JUDGMENT
  Suppose medicine use is safe and effective if:
  1. IndividualCss is on average at the Target Conc
     - Aim for the optimum target
  2. 90% of the time Css is within 80%-125% of Target Conc
     - 'therapeutic range' with optimum target

- STATISTICS
  Assume log-normal distribution for Css
  90% of Css must lie within ± 1.64 x SD
  - Therefore SD must be 0.136
  
  The Safe and Effective Variability (SEV) is 13.6%

Three Ways to Dose

- Population
  » Same dose for everyone
    - The dream dosing method!

- Group (Covariate guided)
  » Same dose for similar group
    - e.g. same weight, CLcr, genotype

- Individual
  » Dose determined by individual response
    - e.g. BP, INR, blood conc
Dosing Individualization Method Depends on Safe and Effective Variability (SEV)
Suppose PPV_{total}=0.7, BSV_u=0.4, WSV_u=0.3
PPV_U=sqrt(BSV_u^2 + WSV_u^2)=0.5
BSV_P=sqrt(PPV_{total}^2 – BSV_u^2)=0.57

<table>
<thead>
<tr>
<th>SEV</th>
<th>Method Criteria</th>
<th>Example</th>
<th>Dosing Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td>SEV&gt;PPV_{total}</td>
<td>0.9&gt;0.7</td>
<td>Population dosing</td>
</tr>
<tr>
<td>0.55</td>
<td>PPV_{total} &gt; SEV SEV&gt;PPV_U</td>
<td>0.7&gt;0.55 0.55&gt;0.5</td>
<td>Group dosing (WT, CLcr, etc) (BSV_U 0)</td>
</tr>
<tr>
<td>0.35</td>
<td>PPV_U &gt; SEV SEV&gt;WSV_U</td>
<td>0.5&gt;0.35 0.35&gt;0.3</td>
<td>Individual response dosing (TCI) (BSV_U 0)</td>
</tr>
</tbody>
</table>

*Suppose PPV_{total}=0.7, BSV_u=0.4, WSV_u=0.3
PPV_U=sqrt(BSV_u^2 + WSV_u^2)=0.5
BSV_P=sqrt(PPV_{total}^2 – BSV_u^2)=0.57

Safe and Effective Variability (SEV) Aminoglycosides

- Suggested Therapeutic Success Criterion
  - 90% of Concs Within 80%-125% of Target Css
  - SEV is 0.136 (log normal SD)
- Unpredictable PPV_U is 0.33 and is > SEV
  - Covariate (WT, CLcr) prediction alone will be inadequate
- Unpredictable WSV_U is 0.13 and is < SEV (just!)
  - TCI can achieve safe and effective target

Know Your Target Be Courageous

- Target for drug development is to learn
  - the concentration effect relationship
  - safe and effective variability
- Target for clinical practice is to confirm
  - Target effect and target concentration
  - Best method for achieving the target effect for the patient
- PKPD provides the tools to achieve the targets
  - time to move away from traditional empirical approaches.
  - drug developers and clinicians must have courage to change
- Take Aim and Hit the Target!
Which Way to Aim?

- Phase 2 Drug Development
  - PK and PKPD relationships (Target Effect → Target Conc)
  - Predictable and Unpredictable variability (PPV<sub>T</sub>)
  - Between (BSV<sub>U</sub>) and within subject (WSV<sub>U</sub>)

- Phase 3 Drug Development
  - Safe and effective variability (SEV)
  - The BIG difficulty is deciding on SEV!

- Clinical Use of Medicines
  - Use quantitative criteria to decide on dosing method
    - Covariate Dosing if PPV<sub>T</sub> > SEV > PPV<sub>U</sub>
    - TCI Dosing if PPV<sub>U</sub> > SEV > WSV<sub>U</sub>

The Target for PKPD

- Pharmacokinetics
- Pharmacodynamics
- Patient Outcome

The target for PKPD is improving patient outcome by developing medicines which can achieve the target effect.

References


Holford NHG, Bursel TM. Safe and effective variability - A criterion for dose individualization. Ther Drug Monit. 2012; 34: 565-68.


