System parameters in clinical pharmacology

Clinical Pharmacology Weekly Seminar
September, 16th 2014

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Model-based approach in clinical pharmacology

Developing and applying mathematical and statistical models to characterize, understand and inform clinical pharmacological processes in order to rationalize decision making in drug development and pharmacotherapy
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Developing and applying mathematical and statistical models to characterize, understand and inform clinical pharmacological processes in order to rationalize decision making in drug development and pharmacotherapy.
CONCEPT
What are the physiological processes we want to describe with our models?

- Each process are characterised by a set of parameters (system and drug parameters)
- Today we will focus on **system parameters**
Focus to understand parameters in our models because...

The ability to differentiate and explain sources of variability for each parameter, which can be induced by extrinsic and/or intrinsic factors, will improve our interpretation of the model results and provide more adequate answers for decision making in drug development and pharmacotherapy.
Objectives for today’s discussion

• How should we define system parameters?
  – Examples of hypothetical situation where we can identify a system parameter

• What are the most common system parameters used in clinical pharmacology?

• How should we interpret these parameters in relation with physiological processes?

• What are the examples of conditions in which these parameters are affected?
  – Sepsis and pregnancy as examples
How should we define system parameter?

- **Parameter:** “a numerical or other measurable factor forming one of a set that defines a system or sets the conditions of its operation”.

- **System parameter:** “parameter that is highly sensitive to (patho-)physiological changes”.
Example of a typical situation in which the system parameter can be clearly identified

• Patient is given the same treatment for two consecutive weeks. As result of disease progression, patient suffers hepatic failure which leads to change in system (i.e. decreased hepatic clearance).

• Change in system leads to change in parameter, i.e. clearance
Example of a typical situation in which the system parameter can be clearly identified

- Patient is given the same treatment for two consecutive weeks. As result of **disease progression**, patient suffers hepatic failure which leads to change in system (i.e. **decreased hepatic clearance**).
- Change in system leads to change in parameter, i.e. clearance
- **Decision:** reduce dose
However, reality is slightly more complex...

- Goal of study was to determine which drug (A or B) would be the best treatment option for disease X
- Healthy volunteer is given daily administration of drug A for a week, followed by a washout period of two weeks. The same study is then repeated in the same volunteer with Drug B
- Pharmacokinetic at Day 1 of each drug was compared with Day 7
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- Pharmacokinetic at Day 1 of each drug was compared with Day 7
- Response was comparable between Drug A and B at Day 1. But Drug B was found to inhibit the CYP450 pathway which lead to decreased hepatic clearance after 1 week
- Decision: Drug A is chosen as standard treatment option
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- Response was comparable between Drug A and B at Day 1. But Drug B was found to inhibit the CYP450 pathway which lead to decreased hepatic clearance after 1 week
- Decision: Drug A is chosen as standard treatment option
- Q1: in this case, both drug and system changed. How should we define hepatic clearance now? As drug and system parameter?
- Q2: aren’t the most model parameters actually hybrid parameters?
What are common system parameters used in clinical pharmacology?

- **Disease**
  - Baseline biomarker level
    - Cardiac output/cardiac index
    - Peak O₂ uptake and CO₂ output
    - Renal/hepatic blood flow
  - Disease slope
  - \( K_{\text{in}} \)
  - \( K_{\text{out}} \)

- **Pharmacokinetic**
  - Clearance
  - Volume of distribution
  - Bioavailability
  - Absorption

- **Drug effect**
  - \( E_{\text{max}} \)
  - \( EC_{50} \)
Total body clearance may be viewed as the volume of plasma from which drug is totally removed over a specified period.

Cannot exceed the organ blood flow (liver = 90 L/h; kidney = 70 L/h)

Exception applies, for example when there is an additional elimination pathway next to the hepatic/renal clearance.
VOLUME OF DISTRIBUTION
Volume of distribution represents a theoretical volume into which the drug would have to distribute to achieve the measured concentration.

Figure 1. The principle of volume of distribution.

With Drug A, the measured concentration in the sampling compartment is 10 mg/l, therefore the volume is estimated at 10 litre (100 mg/10 mg/l). Drug B is highly bound to plasma proteins, therefore the measured concentration of 100 mg/l results in an estimated volume of 1 litre. Drug C is extensively distributed into the tissues and the measured concentration of 1 mg/l gives an apparent volume of 100 litre.
Where can we find fluid in the body?

- Intracellular fluid (ICF)
- Interstitial fluid
- Extracellular fluid (ECF)
- Plasma (intravascular fluid)
Fluid distribution in a typical 70 kg adult

<table>
<thead>
<tr>
<th>V (L)</th>
<th>Drug distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>15-18</td>
<td>Extracellular fluid</td>
</tr>
<tr>
<td>40-50</td>
<td>All body water</td>
</tr>
<tr>
<td>&gt;&gt;50</td>
<td>Tissue</td>
</tr>
</tbody>
</table>

Neonates and young children have higher proportion of body water per body weight.
CARDIAC OUTPUT/INDEX
Definition of cardiac output and cardiac index

- Cardiac output (CO) is the volume of blood being pumped by the heart in the time interval of one minute, measured by stroke volume (SV) and heart rate (HR).
- Cardiac index (CI) relates cardiac output to body surface area (BSA).
- Both are relevant parameters as increased CO/CI could indicate increased drug elimination.

\[
CI = \frac{CO}{BSA} = \frac{SV \times HR}{BSA}
\]
EXAMPLE 1: SEPSIS
Sepsis as example of how pathophysiological changes can complicate adequate treatment

• Treatment of sepsis remains a major challenge
• Physiology of patients with sepsis may change over a short period of time with consequent effect on PK/PD properties of antibiotics
• Appropriate understanding of how to adjust treatment to changes in PK/PD properties of antibiotics is therefore essential to maximise response
Different stages leading to sepsis

Table 1
SIRS and sepsis definition (ACCP/SCCM-criteria)

<table>
<thead>
<tr>
<th>SIRS (Systemic Inflammatory Response Syndrome)</th>
<th>2 or more of the following criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Temperature &gt; 38°C or &lt; 36°C</td>
</tr>
<tr>
<td></td>
<td>Heart rate &gt; 90 beats/min</td>
</tr>
<tr>
<td></td>
<td>Respiratory rate &gt; 20 breaths/min or PaCO₂ &lt; 32 mm Hg (&lt;4.3 kPa)</td>
</tr>
<tr>
<td></td>
<td>WBC &gt; 12 000 cells/μL or &lt; 4 000 cells/μL or &gt; 10% immature (band) forms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sepsis</th>
<th>Documented infection together with 2 or more SIRS criteria</th>
</tr>
</thead>
</table>

| Severe Sepsis | Sepsis associated with organ dysfunction, including, but not limited to, lactic acidosis, oliguria, hypoxemia, coagulation disorders, or an acute alteration in mental status. |

| Septic Shock | Sepsis with hypotension, despite adequate fluid resuscitation, along with the presence of perfusion abnormalities. Patients who are on inotropic or vasopressor agents may not be hypotensive at the time when perfusion abnormalities are detected. |
Effects of pathophysiological changes during sepsis

Stimulated by increased production of endogenous mediators (interleukins, cytokines, platelet activating factors etc) → increased vasodilatation → reduced blood pressure and increased blood flow/cardiac output

Caused by myocardial depression, characterized by cardiac output that fails to meet metabolic demands

In particular applicable for hydrophilic drugs due to fluid shifts from intravascular to interstitial fluid → undesirable effect given that bacteria are present in blood!

Initial stage sepsis
- Increased cardiac index
  - Increased clearance
  - Low serum concentrations

Progressed sepsis
- Leaky capillaries and/or altered protein binding
  - Increased volume of distribution
  - High serum concentrations
- End-organ dysfunction (e.g. renal or hepatic)
  - Decreased clearance
EXAMPLE 2: PREGNANCY
## Physiological changes during pregnancy

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Change during pregnancy</th>
<th>Normal pregnancy values</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>Increases 15–20 bpm</td>
<td>75–95 bpm</td>
</tr>
<tr>
<td>Cardiac output</td>
<td>Increases 30–50%</td>
<td>5.5 l/min</td>
</tr>
<tr>
<td>Mean arterial blood pressure</td>
<td>Decreases 10 mmHg in third trimester</td>
<td>80 mmHg</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>Decreases 10–15%</td>
<td>1200–1500 dynes/s/cm²</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tidal volume</td>
<td>Increased 40%</td>
<td>700 ml</td>
</tr>
<tr>
<td>Minute ventilation</td>
<td>Increased 40%</td>
<td>10.5 l/min</td>
</tr>
<tr>
<td>Expiratory reserve volume</td>
<td>Decreased 15–20%</td>
<td>550 ml</td>
</tr>
<tr>
<td>Functional residual capacity</td>
<td>Decreased 20–25%</td>
<td>1350 ml</td>
</tr>
<tr>
<td><strong>Blood gas</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>Unchanged</td>
<td>7.4–7.45</td>
</tr>
<tr>
<td>pCO₂</td>
<td>Decreased</td>
<td>27–32 mmHg</td>
</tr>
<tr>
<td>pO₂</td>
<td>Increased</td>
<td>100–108 mmHg</td>
</tr>
<tr>
<td>HCO₃</td>
<td>Decreased</td>
<td>18–21 meq/l</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blood volume</td>
<td>Increases 30–50%</td>
<td>4500 ml</td>
</tr>
<tr>
<td>Erythrocyte volume</td>
<td>Increases 10–15%</td>
<td></td>
</tr>
<tr>
<td>Hematocrit</td>
<td>Decreased</td>
<td>32–34%</td>
</tr>
<tr>
<td>White blood cell count</td>
<td>Increased</td>
<td>5000–15,000/mm³</td>
</tr>
<tr>
<td>Factors I, II, V, VII, VIII, IX, X and XII</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>Increased</td>
<td>&gt;400 mg/dl</td>
</tr>
<tr>
<td><strong>Genitourinary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal blood flow</td>
<td>Increased 50–60%</td>
<td>700 ml/min</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>Increased 60%</td>
<td>140 ml/min</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>Decreased</td>
<td>&lt;0.8 mg/dl</td>
</tr>
<tr>
<td>Serum urea nitrogen</td>
<td>Decreased</td>
<td>&lt;13 mg/dl</td>
</tr>
</tbody>
</table>

Source: Women's Health © 2009 Future Medicine Ltd
Effect of physiological changes during pregnancy

- **Progesterone production** → decreased gastric emptying and intestinal motility
- **Increase in gastric pH** → decreased absorption of some weak acids such as some protease inhibitors and non-nucleoside reverse transcriptase inhibitor (NNRTI)
- **Increase of total body water and body fat** → increased volume of distribution of both hydrophilic and lipophilic drugs
- **Haemodilution** → decreased albumin and α₁-acid glycoprotein (AAG) concentration which consequently increases amount of unbound drug as result of decreased protein binding
- **Induction of CYP450 enzymes** by estrogen/progesterone, **increase of renal blood flow and glomerular filtration** → increased hepatic/renal excretion
Total body clearance

• Describes the removal of drug from a volume of plasma in a given time period (expressed as volume/time)
• Very important as it informs how target concentration/dose rate could be maintained
• Determined by extraction ratio and organ blood flow
  – Extraction ratio reflects the organ’s ability to remove a drug
  – Organ blood flow reflects the volume of blood delivered to the organ per unit time
  – Blood flow (kidney = 70 L/h; liver = 90 L/h) is the upper limit of organ clearance
Model for organ clearance of a drug

\[ E = \frac{C_{in} - C_{out}}{C_{in}} \]

\[ CL_{\text{organ}} = Q \times E \]

E = extraction ratio; 0 (no drug removed) ≤ E ≤ 1 (all drug removed)
Q = blood flow
\( C_{in} \) = drug concentration in the blood flowing into the organ
\( C_{out} \) = drug concentration in the blood flowing out of the organ
Volume of distribution of beta-lactams in healthy volunteers and septic ICU patients

Figure 3: Heterogeneity of volume of distribution in litres of β-lactam antibiotics in ICU patients. Open circles: volume of distribution in healthy volunteers [44,51,89-92]; filled squares: weighted means of volume of distribution in the studies; straight lines: ranges of the means of volume of distribution in the studies.
Different antibiotics classes have different type of bacterial kill characteristics

![Pharmacokinetic and pharmacodynamic parameters of antibiotics on a concentration vs time curve. AUC = area under the serum concentration-time curve; C_max = peak serum drug concentration; C_min = minimum serum drug concentration; MIC = minimum inhibitory concentration; T>MIC = time for which the serum concentration of a drug remains above the MIC for a dosing period.]

**Table 1. Pharmacodynamic properties that correlate with the efficacy of selected antibacterials**

<table>
<thead>
<tr>
<th>Antibacterials</th>
<th>Pharmacodynamic kill characteristics</th>
<th>Optimal pharmacodynamic parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Concentration dependent</td>
<td>C_max/MIC</td>
</tr>
<tr>
<td>Metronidazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Concentration dependent</td>
<td>AUC24/MIC</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>with time dependence</td>
<td></td>
</tr>
<tr>
<td>Tetracyclines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glycopeptides</td>
<td></td>
<td></td>
</tr>
<tr>
<td>β-Lactams</td>
<td>Time dependent</td>
<td>T&gt;MIC</td>
</tr>
<tr>
<td>Carbapenems</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linezolid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
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</tbody>
</table>

**AUC24 = area under serum concentration-time curve during 24-hour time period; C_max = peak plasma drug concentration; MIC = minimum inhibitory concentration; T>MIC = time for which the serum concentration of a drug remains above the MIC for a dosing period.**
Antibiotics have different classifications based on solubility and PK/PD properties

Site of action (intracellular versus extracellular) determines choice of antibiotic
How does changes in V and CL affect antibiotics exposure in septic patients?

“Healthy”

V ↑
CL ↔
C<sub>max</sub> ↓
AUC<sub>T</sub> ↔
T > MIC ↑
How does changes in V and CL affect antibiotics exposure in septic patients?

“Healthy”

V \uparrow
CL \leftrightarrow
C_{\text{max}} \downarrow
AUC_T \leftrightarrow
T > MIC \uparrow

V \leftrightarrow
CL \uparrow
C_{\text{max}} \downarrow
AUC_T \downarrow
T > MIC \downarrow

Increased V may not affect efficacy as long CL does not change for drugs of which AUC_T is the best predictor for efficacy