The general Concepts of Pharmacokinetics

- $C_{\text{max}}$, AUC, clearance, half-life, etc...
- interrelations among PK parameters
- protein binding and tissue accumulation
- examples with $\beta$-lactams (including ertapenem), fluoroquinolones (moxifloxacin), and macrolides (telithromycin)

This part uses material from presentations by H. Derendorf (Gainesville, Fla.) made at the 2001 and 2001 ISAP Educational Workshops
What is pharmacokinetics?

- "what the body does to the drug"

- the fate of the drug in terms of:
  - Liberation
  - Absorption
  - Distribution
  - Metabolism
  - Excretion

- the time course of drug and metabolite concentrations in the body
What is pharmacokinetics (PK) for?

In its first inception, PK has been developed to help optimizing drug therapy with respect to:

- dose
- dosage regimen
- dosage form

But in a second inception, PK can be considered as the way by which the drug can be made useful ...

- does it reach the target in sufficient amounts
- for long enough
- does it each non-desired targets?
Key pharmacokinetic parameters ...

- Clearance (Cl)
- Volume of distribution ($V_d$)
- Half-life ($t_{1/2}$)
- Bioavailability
- Area under the curve (AUC)
- Protein Binding
Clearance (CI)

- quantifies **ELIMINATION**
- is the volume of body fluid cleared per time unit (L/h, mL/min)
- is usually constant in a given physiopathological situation
- is a **primary** parameter
Clearance (CI)

Eliminating Organ

Quantity eliminated per unit of time

\[ Q \]

\[ C_i \rightarrow Q \rightarrow C_o \]

\[ C_o < C_i \]

extraction

\[ E = \frac{C_i - C_o}{C_o} \]

the rate at which the drug will be excreted is proportional to
- the blood flow in the eliminating organ \( (Q) \)
- the extraction the organ is capable of \( (E) \)

the clearance is thus \( Q \times E \) (= L/h or ml/min)
Which parameters influence the clearance?

- blood flow
- intrinsic clearance
- drug availability for the clearance mechanism

\[
Cl = Q \times E
\]

- high extraction drugs: \( E \approx 1 \)
  \[ Cl \approx Q \]

- low extraction drug (\( E << 1 \))
  - protein binding (reduces free drug)
  - no transport by the eliminating organ
  \[ Cl << Q \]
What is the significance of the clearance?

- A drug with a fast clearance will not stay around for long … and may require readministration…

- But a drug with a slow clearance may be bound to proteins and unavailable (see later …)

- If clearance falls during treatment (or is abnormally low at the beginning of treatment), patient will be overdosed!!
How do we determine the clearance?

- Directly from the measurement of the excretion rate
  - easy if only one eliminating organ (kidney, e.g.)
  - but drugs may be cleared by many organs (total clearance = sum of individual clearances)

- Indirectly from the ratio of the dose administered and the AUC (see later)
Volume of distribution ($V_d$)

- Quantifies the **DISTRIBUTION** (i.e. how the drug has access to the various compartments of the body)
- relates drug concentration ($C$) in the blood to the amount of drug that has been introduced in the body (= Dose)

$$V_d = \frac{\text{Dose}}{\text{Concentration in blood}}$$

- is also a **primary** parameter
- but may be an apparent volume ...
What is $V_d$?

$V_d = D / C_1$

$V_d = 1 \text{ L/kg}$

if $D$ in $\text{g/g}$

$C_2 >> C_1$

$V_d = D / C_2$

$V_d < 1 \text{ L/kg}$

if $D$ in $\text{g/g}$

$C_3 << C_1$

$V_d = D / C_3$

$V_d > 1 \text{ L/kg}$

if $D$ in $\text{g/g}$

Storage

No access
<table>
<thead>
<tr>
<th>if found in</th>
<th>L/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>serum only</td>
<td>0.1</td>
</tr>
<tr>
<td>→ dicloxacillin</td>
<td></td>
</tr>
<tr>
<td>serum plus extracellular fluids</td>
<td>0.25</td>
</tr>
<tr>
<td>→ gentamicin</td>
<td></td>
</tr>
<tr>
<td>total body fluids</td>
<td>0.60</td>
</tr>
<tr>
<td>→ antipyrine</td>
<td></td>
</tr>
<tr>
<td>in fluids plus moderate accumulation in tissues</td>
<td>1.8</td>
</tr>
<tr>
<td>→ ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td>in fluids plus marked accumulation in tissues</td>
<td>31</td>
</tr>
<tr>
<td>→ azithromycin</td>
<td></td>
</tr>
</tbody>
</table>
What is the significance of the Vd?

• A drug with a small $V_d$ will have high initial blood levels ...

• A large Vd will cause low initial blood levels ...
  – if it is patient related, you need to give more of the drug (e.g., burn patients)
  – if it is drug-related, the drug cannot be too concentration-dependent ... and it may become ineffective in blood-related (invasive) infections
Half-life ($t_{1/2}$)

- Half-life is the time it takes for the concentration to fall to half of its previous value.
- This is a parameter which is easy to measure, (just take a few blood samples…) BUT …
- It is secondary pharmacokinetic parameter because it depends on both clearance and volume of distribution.
Why is half half-life a secondary parameter

You start from here, but …
this is $C_{\text{max}}$, i.e. Dose / $V_{\text{dis}}$

And you follow a slope which is dictated by the drug elimination rate, i.e the total body clearance
Why is half half-life a secondary parameter?

\[ t_{1/2} = \frac{0.693 \cdot Vd}{CL} \]
What is useful in half-life?

- Direct information as how serum concentrations will fall over time and reach a pre-set threshold if you know the $C_{max}$ (i.e. your starting point).

- Direct, practical comparisons between drugs if sharing the same $V_d$ ...

You can compare $\beta$-lactams between themselves, e.g. but you CANNOT compare $\beta$-lactams and azithromycin, e.g.
Area under the Curve (AUC)

AUC = Dose / Clearance

Peak

trough

area under the curve
Area under the Curve (AUC)

• Useful to assess the total drug exposure
• but profoundly influenced by
  – the Vd (height of the curve)
  – the clearance (rate of elimination)
• advantage: it combines the two primary parameters so that the final value is relatively stable and independent of the mode of administration ...
## Interrelations between secondary PK parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>influenced by</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt;</td>
<td>+ dose *</td>
</tr>
<tr>
<td></td>
<td>– clearance</td>
</tr>
<tr>
<td></td>
<td>– V&lt;sub&gt;d&lt;/sub&gt;</td>
</tr>
<tr>
<td>half-life:</td>
<td>– clearance</td>
</tr>
<tr>
<td></td>
<td>+ V&lt;sub&gt;d&lt;/sub&gt;</td>
</tr>
<tr>
<td>AUC:</td>
<td>+ dose **</td>
</tr>
<tr>
<td></td>
<td>– clearance</td>
</tr>
</tbody>
</table>

+ directly proportional
- indirectly proportional
* unit dosis
** total dose for the period considered (usually 24h)
Bioavailability

• quantifies **ABSORPTION** towards the blood
• is measured by comparing oral (or another mode of administration) to intravenous administration

\[
F = \frac{AUC_{po}}{AUC_{iv}}
\]

• but the rate is also important ...
A low bioavailability reduces $C_{\text{max}}$ and AUC.
The rate of bioavailability may also influence $C_{\text{max}}$ and $T_{\text{max}}$. 

![Graph showing concentration over time with peaks for $C_{\text{max}}$ and $T_{\text{max}}$.]
Protein Binding

- reversible vs. irreversible
- linear vs. nonlinear
- rapid equilibrium

The free (unbound) concentration of the drug at the receptor site should be used in PK/PD correlations to make prediction for pharmacological activity.
Protein binding decreases activity of antibiotics

**Effect of Protein Binding on Antimicrobial Activity**

MICs of Staphylococcus aureus (Data from Kunin et al. (1973))

- **MIC Broth**
- **MIC Serum**
- **$f_b$ for MIC Serum**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>$f_b$</th>
<th>MIC Serum</th>
<th>MIC Broth</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMPI</td>
<td>0.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>METHI</td>
<td>0.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BENZ</td>
<td>0.65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAF</td>
<td>0.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OXA</td>
<td>0.93</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLOXA</td>
<td>0.95</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
It is the free drug that acts ...

vascular space

extravascular space

plasma protein binding

blood cell binding, diffusion into blood cells, binding to intracellular biological material

tissue cell binding, diffusion into tissue cells, binding to intracellular biological material

binding to extracellular biological material

It is the free drug that acts ...
A couple of examples...

- Ertapenem, a long acting penem …
- Comparisons among fluoroquinolones
- Why has telithromycin been selected?
imipenem $\rightarrow$ meropenem $\rightarrow$ ERTAPENEM

- Stability to $\beta$-lactamases
- Resistance to dehydropeptidase
- Binding to proteins
- Change in spectrum

<table>
<thead>
<tr>
<th></th>
<th>Gram (-)</th>
<th>P. aer.</th>
<th>Gram (+)</th>
<th>anaer.</th>
<th>$t_{1/2}$ (h)</th>
<th>res. to renal hydrolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMI</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>MERO</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>1</td>
<td>+</td>
</tr>
<tr>
<td>ERTA</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>4</td>
<td>+</td>
</tr>
</tbody>
</table>

GRAM (-)  | P. aer.  | Gram (+) | anaer. | $t_{1/2}$ (h) | res. to renal hydrolysis |
---------|----------|----------|--------|--------------|--------------------------|
IMI      | +        | +++      | +++    | 1            | -                        |
MERO     | ++       | +++      | ++     | 1            | +                        |
ERTA     | ++       | +        | ++     | 4            | +                        |
Ertapenem serum concentration in volunteers

range of serum concentrations = 150 → 1 mg/L for a daily dose of 1 g

Majumdar et al, AAC 2002, 46: 3506-3511
binding to serum proteins: to be linear or not...

Free fraction = 5 - 10 % for a daily dose of 1 g

Majumdar et al., AAC 2002, 46: 3506-3511
Protein binding impairs tissue distribution...

TOTAL drug concentration measured after 3 days

data submitted to the FDA for product registration
But protein binding does prolong half-life

<table>
<thead>
<tr>
<th></th>
<th>Cmax (mg/l)</th>
<th>prot. binding (%)</th>
<th>T_{1/2} (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ertapenem</td>
<td>160</td>
<td>90-95</td>
<td>4</td>
</tr>
<tr>
<td>ceftriaxone</td>
<td>180</td>
<td>83-96</td>
<td>7</td>
</tr>
</tbody>
</table>

Paradis et al., AAC 1992, 36: 2085-2092
### Fluoroquinolones: bioavailability (p.o.) and $C_{\text{max}}$

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/24h)</th>
<th>Bioav. (%)</th>
<th>$C_{\text{max}}$ (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>norfloxacin</td>
<td>800</td>
<td>~ 35</td>
<td>2.4 *</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500</td>
<td>~ 70</td>
<td>2.4 *</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>~ 95</td>
<td>3-4.5 *; +</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>~ 99</td>
<td>5-6 *; +</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>~ 90</td>
<td>4.5 *</td>
</tr>
</tbody>
</table>

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, and AVELOX®
+ first dose to equilibrium

This is better

But what about this?
### 24h-AUC / MIC of fluoroquinolones (p.o.)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage (mg/24h)</th>
<th>24h-AUC (mg/L x h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>norfloxacin</td>
<td>800</td>
<td>14 *, #</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>500</td>
<td>12 *</td>
</tr>
<tr>
<td>ofloxacin</td>
<td>400</td>
<td>31 to 66 *, +</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>500</td>
<td>47 *</td>
</tr>
<tr>
<td>moxifloxacin</td>
<td>400</td>
<td>48 *</td>
</tr>
</tbody>
</table>

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, and AVELOX®
# literature data
+ first dose to equilibrium

**poor if MIC is ↑

Much better !!
The Pharmacokinetics of telithromycyn, as submitted to the FDA (April 2001):

<table>
<thead>
<tr>
<th></th>
<th>800 mg (single dose)</th>
<th>800 mg (7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;max&lt;/sub&gt; (mg/L)</td>
<td>1.9 (42)</td>
<td>2.3 (31)</td>
</tr>
<tr>
<td>C&lt;sub&gt;24h&lt;/sub&gt; (mg/L)</td>
<td>0.03 (45)</td>
<td>0.07 (72)</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;24h&lt;/sub&gt; (mgxh/L)</td>
<td>8.3 (31)</td>
<td>12.5 (43)</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; (h)</td>
<td>7.2 (39)</td>
<td>9.8 (20)</td>
</tr>
</tbody>
</table>

Data is mean (% CV) for n=18

This was to be a once-a-day drug ...

http://www.fda.gov/ohrms/dockets/ac/01/slides/3746s_09_aventis/
Pharmacokinetics

This where we are ...

Dosing → Concentration in blood

Concentration at site of infection

Concentration in non-target tissues

Got it?