The general Concepts of Pharmacokinetics

What is this jargon?
Is it useful?

- $C_{\text{max}}$,
- clearance,
- $Vd$,
- half-life,
- AUC,
- bioavailability,
- protein binding

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With some slides from H. Derendorf (University of Florida)
Pharmacokinetics (PK) is speed!
What is pharmacokinetics?

- "what the body does to the drug"

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

- the time course of drug and metabolite concentrations in the body
What is pharmacokinetics?

• "what the body does to the drug"

• The fate of the drug in terms of:
  – Absorption
  – Distribution
  – Metabolism
  – Excretion

• The time course of drug and metabolite concentrations in the body

Pharmacokinetics = conc. vs time
What is PK for?

PK is the way to see if the drug can be made useful …

• does it reach the **target** in sufficient amounts?

• for **long enough**?

• does it each **non-desired targets**?
The $C_{\text{max}}$ is the highest concentration in plasma after administration ...
$C_{\text{max}}$ ... is proportional to the dose ...

dose $= 1$

dose $= 2$
What is the significance of the $C_{\text{max}}$?

- A drug with a (too) low $C_{\text{max}}$ may be ineffective if its activity is concentration-dependent.

- A drug with a (too) high $C_{\text{max}}$ may become toxic if toxicity is related to $C_{\text{max}}$ (this NOT always the case.... !)

- You have to adjust the dose to get the appropriate $C_{\text{max}}$. !
Eliminating Clearance (Cl)

Quantity eliminated per unit of time

\[ Q \] (quantity eliminated per unit of time)

\( C_i \) (in)

\( C_o \) (out)

\( C_o < C_i \)

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)
Clearance

Clearance can be calculated from

- **Excretion rate / Concentration**
  
  e.g. \((\text{mg/h}) / (\text{mg/L}) = \text{L/h}\)

- **Dose / Area under the curve (AUC)**
  
  e.g. \(\text{mg} / (\text{mg}\cdot\text{h/L}) = \text{L/h}\)
Clearance

Total body clearance is the sum of the individual organ clearances

$$CL = CL_{\text{renal}} + CL_{\text{hepatic}} + CL_{\text{other}}$$
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 may show a slow clearance because it is bound to proteins and therefore largely unavailable (see later …)

- If clearance falls during treatment (or is abnormally low at the beginning of treatment), patient will be overdosed!!
Volume of distribution ($V_d$)

- Quantifies 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)

\[
V_d = \frac{\text{Dose}}{\text{Concentration in blood}}
\]
What is $V_d$?

Think about the body as a large "bag" with compartments in which you drop a drug ...
What is $V_d$?

If drug diffuses throughout the body ...

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

serum concentration = tissue concentration
What is $V_d$?

If the drug reaches only the plasma and the extracellular fluids ...

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

$C_{\text{max}} \uparrow$

high serum concentration

no or little tissue concentration
What is $V_d$?

If drug accumulates in tissues...

- $V_d > 1 \text{ L/kg}$
- $C_{\text{max}} \downarrow$

- low serum concentration
- high tissue concentration
Typical volumes of distribution of antibiotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume (L/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>dicloxacillin</td>
<td>0.1</td>
</tr>
<tr>
<td>(serum only)</td>
<td></td>
</tr>
<tr>
<td>gentamicin</td>
<td>0.25</td>
</tr>
<tr>
<td>(serum plus extracellular fluids)</td>
<td></td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>1.8</td>
</tr>
<tr>
<td>(fluids plus moderate accumulation in tissues)</td>
<td></td>
</tr>
<tr>
<td>azithromycin</td>
<td>31</td>
</tr>
<tr>
<td>(marked accumulation in tissues)</td>
<td></td>
</tr>
</tbody>
</table>
What is the clinical significance of the Vd?

- A drug with a small $V_d$ will have high initial blood levels but will not reach tissues...

- A large $V_d$ will cause low initial blood levels ...
  - if patient-related, you will need to give more of the drug (e.g., burn patients)
  - if drug-related, 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 the clearance AND the volume of distribution
Why is half half-life a secondary parameter?

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

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

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

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

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

You can compare $\beta$-lactams between themselves for half-life, ...

BUT you CANNOT compare $\beta$-lactams (low $V_d$) and azithromycin (high $V_d$), e.g.
Area under the Curve (AUC)

AUC = dose / clearance

peak

trough

area under the curve
Area under the Curve (AUC)

• combines
  – one parameter directly linked to the medical decision: **the dose of the drug**!
  – one parameter linked to the drug AND the patient: **the clearance** ...

• its value is **independent** of the scheme of administration ...

• useful to assess the **total** drug exposure
Determination of the AUC

\[ AUC = \sum_{i=1}^{n} \frac{(C_i + C_{i-1})}{2} \cdot (t_i - t_{i-1}) \]
### 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®

# litterature data

+ first dose to equilibrium

Much better!!

Poor if MIC is ↑

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UCL PK/PD Course
Bioavailability

- quantifies **ABSORPTION** from the site of administration **to the blood**
- is measured by comparing oral (or another mode of administration) to intravenous administration

A poor bioavailability reduces both $C_{\text{max}}$ and AUC ... and thereby decreases the potential for efficacy !!!
A low bioavailability (F) reduces both $C_{\text{max}}$ and AUC.
Fluoroquinolones: influence of cations on bioavailability

- A. Cipro 750 mg
- B. + 850 mg CaCO₃
- C. + 600 mg Al(OH)₃

<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>

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* first dose to equilibrium
Protein binding: it is (almost always) the free drug that acts ...

Effect of Protein Binding on Antimicrobial Activity

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

MIC [µg/ml]

0 1 2 3 4 5 6 7 8

AMPI METHI BENZ NAF OXA CLOXA

\( f_b \): 0.22 0.37 0.65 0.90 0.93 0.95

MIC Broth

MIC Serum

\( C_f \) for MIC Serum
Protein binding: it is (almost always) the free drug that acts ...

vascular space

plasma protein binding

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

extravascular space

binding to extracellular biological material

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

Dialysate

Perfusate

Interstitium

Capillary

Cell
Microdialysis
Protein binding impairs and slows down drug distribution...

TOTAL drug concentration of ertapenem (a high protein bound β-lactam) in plasma and blister fluid after 3 days of treatment
But protein binding prolongs half-life ...
Two-compartment model

Dose

$X_c$ Drug in the central compartment

$X_p$ Drug in the peripheral compartment

$E$ Drug eliminated

$k_{10}$

$k_{12}$

$k_{21}$
Two-compartment model
A typical example for a $\beta$-lactam

Laterre et al, JAC 2015, 70:891–898
Three-compartment model

- **D** Dose
- **E** Drug eliminated
- **X_c** Drug in the central compartment
- **X_{ps}** Drug in the shallow peripheral compartment
- **X_{pd}** Drug in the deep peripheral compartment
Three-compartment model

\[ C = a \cdot e^{-\alpha t} + b \cdot e^{-\beta t} + c \cdot e^{-\gamma t} \]

\( \alpha \)-phase: distribution phase
\( \beta \)-phase: rapid elimination phase
\( \gamma \)-phase: slow elimination phase
Three-compartment model

The example of oritavancin … single dose treatment!

![Graph showing concentration over time]

1 week

1 month
PHARMACOKINETICS

what the body does to the drug

PHARMACODYNAMICS

what the drug does to the body
Pharmacokinetics
conc. vs time

Pharmacodynamics
conc. vs effect

PK/PD
effect vs time