What is this jargon?
Is it useful?

With the support of Wallonie-Bruxelles-International
Pharmacokinetics is speed!
The general Concepts of Pharmacokinetics (PK)

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

Let us travel together!!
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 \textbf{target} in sufficient \textbf{amounts}?

• for \textbf{long enough}?

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

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 Organ Clearance (Cl)

Quantity eliminated per unit of time

\[ Q \]

the clearance is thus \( Q \times E (= \text{L/h or ml/min}) \)

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)

\[ C_o < C_i \]
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 ...

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

$C_{\text{max}} = \text{dose /weight}$

serum concentration = tissue concentration
What is $V_d$?

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

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

$C_{\text{max}} > \text{dose/weight}$

D

high serum concentration

no or little tissue concentration
What is $V_d$?

If drug accumulates in tissues...

$V_d > 1 \text{ L/kg}$
$C_{\text{max}} < \text{dose / weight}$

low serum concentration

high tissue concentration
## Typical volumes of distribution of antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>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 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
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
### 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>
<tr>
<td></td>
<td></td>
<td><strong>Poor if MIC is</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Much better!!</strong></td>
</tr>
</tbody>
</table>

* US prescrib. inf. (adult of 60 kg) of NOROXIN®, CIPRO®, FLOXIN®, LEVAQUIN®, and AVELOX®

# litterature data

+ first dose to equilibrium
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: 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>

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* first dose to equilibrium
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

(binding to extracellular biological material)
Protein binding impairs and slows down drug distribution...

TOTAL drug concentration of ertapenem (a high protein binding \(\beta\)-lactam) in plasma and blister fluid after 3 days of treatment.
But protein binding prolongs half-life ...

Ertapenem 1 g

Ceftriaxone 1 g

concentration (mg/l)

Concentration vs. time (h)

Paradis et al, AAC 1992, 36: 2085-2092

ceftriaxone data: Paradis et al, AAC 1992, 36: 2085-2092
Pharmacokinetics

Dosing → Concentration in blood

Concentration at site of infection

Concentration in non-target tissues

Got it?

Section 3A