PK-PD
Pharmacokinetics-
Pharmacodynamics

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Fellowship critical care
24 October 2011
PK-PD

- Definitions
- Relationship
- Relevance
- Pharmacokinetic parameters
- Pharmacodynamic parameters
- PK-PD and ...
Definitions

• PK = Pharmacokinetics
  – relationship between the dose administered and the changes in the drug concentration in the body with time. (Measured by drug concentration in blood, plasma, tissue)
  – ADME
    • Absorption
    • Distribution
    • Metabolism
    • Elimination

• PD = Pharmacodynamics
  – relationship between drug concentration and its pharmacologic effect (Effects of a drug on the body / disease)

• PK is a determinant of PD
Relevance

• Summarises behaviour of a drug in the body
• Seeks to understand the sources of variability of this behaviour
• Ideally provides the knowledge to prescribe individualised dosing regimes
Pharmacokinetic parameters

- Volume of distribution
- Clearance
- Half-life
- Cmax
- Cmin
- AUC 0-24
Pharmacokinetic parameters

<table>
<thead>
<tr>
<th>PK Parameter</th>
<th>Definition</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Clearance (CL)</td>
<td>The volume of blood cleared of drug per unit time</td>
<td>CL measures the irreversible elimination of a drug from the body by excretion and/or metabolism</td>
</tr>
<tr>
<td>Volume of distribution (V_d)</td>
<td>Apparent volume of fluid that contains the total drug dose administered at the same concentration as in the plasma</td>
<td>V_d is the parameter that relates the total amount of drug in the body to the plasma concentration</td>
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<tr>
<td>Half-life (t_{1/2})</td>
<td>Time required for the plasma drug concentration to decrease by half</td>
<td>Half-life is dependent on CL and V_d; half-life is increased with a decrease in CL or an increase in V_d</td>
</tr>
<tr>
<td>C_{max}</td>
<td>Peak drug concentration during a dosing interval</td>
<td></td>
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<tr>
<td>C_{min}</td>
<td>Minimum drug concentration during a dosing interval</td>
<td></td>
</tr>
<tr>
<td>AUC_{0-24}</td>
<td>Area under the concentration-time curve from 0 to 24 h</td>
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Pharmacokinetic considerations

- Absorption
- Distribution
- Metabolism
- Elimination

\[
\text{Clearance} \quad \{ \text{Absorption, Distribution, Metabolism, Elimination} \}
\]
Routes of drug administration in ICU

• Oral
  – Traditionally avoided
  – Increasing trend to resume oral medication ASAP
  – Some commonly used drugs have no suitable parenteral equivalent

• Subcutaneous and intramuscular
  – Unpredictable bloodflow at the site of injection
  – Insuline/LMWH

• Intravenous
  – Convenient, titratable, reliable, fast way
  – Absorbing of drugs by plastic/glass/ruber
  – precipitation
Volume of distribution

- Applied per organ / total body
- Physiological spaces
  - Intravascular space 3%
    - Endothelium (Size)
  - Interstitial space 1/3
    - Parenchymal cell membranes, lipid barrier (Ionization)
  - Intracellular space 2/3
- Rate of distribution = Half life of organ equilibration
  - Flow-limited
  - Membrane limited (eg morphine uptake into the brain)
Volume of distribution

• Can provide information about the location of a drug in the body
  – Indocyanine Green (0.075 l/kg)
  – Furosemide (0.2l/kg)
  – Antipyrine (0.6 l/kg)
Clearance

• In an organ
  – Liver:
    • Transport to bile
    • Metabolise
      – Phase I: Oxidation or Reduction Cytochrome P450
      – Phase II: Conjugation to form a glucuronide or sulphate
  – Kidney
    • Filtration
    • Active secretion

• For an organ, the clearance = Q X E
  – Q = blood flow through the organ
  – E = Extraction ratio of the drug across the organ
Hepatic Drug Clearance

• High Extraction ratio drugs \( E > 0.7 \)
  - Excess of enzymes that metabolise the drug
  - Rate limiting step is supply of the drug to the liver
  - Hepatic clearance
    \( \approx \) hepatic blood flow
    \( \neq \) amount of active enzyme
    \( \neq \) changes in free drug fraction

• Intermediate extraction ratio drugs

• Low extraction ratio drugs \( E < 0.3 \)
  - Shortage of enzymes that metabolise the drug
  - Rate limiting step is activity of the enzymes
  - Hepatic clearance
    \( \approx \) amount of active enzyme
    \( \approx \) changes in free drug fraction
    \( \neq \) hepatic blood flow
Renal Drug Clearance

• Glomerular filtration
  – Normal 100 ml/min

• Tubular secretion
  – Up to 1.2 L/min = renal bloodflow

• Tubular reabsorption
  – Lipophilic + uncharged 0ml/min
Half-life

\[
t_{1/2} = \frac{0.693 \times V_d}{CL}
\]
Interpreting Half-lives

• The simplicity is appealing but,
• Drugs can have more than 1 half-life
  – Mixing in blood
  – Distribution
  – Elimination
• The measured half-life depends on the study design
  – Frequency bloodsamples
  – Assay dependent
  – Arterial vs venous
• Half lives are not a constant
Pharmacodynamic parameters

• Dose-Response relationships
• Therapeutic index
Dose – Response relationship

• The numbers of receptors
• The willingness of a drug to associate with a receptor = receptor affinity
• The presence of other compounds competing for the binding site on the receptor = agonist / antagonist
• The concentration of the free drug in the vicinity of the receptor = pharmacokinetics
Dose – Response relationship

Dose-Response Curves for the Analgesic and Depressant Effects of Morphine

- Dose-response curve for the analgesic effect of morphine
- Dose-response curve for the depressive effect of morphine on respiration

Margin of safety
The therapeutic index (also known as therapeutic ratio), is a comparison of the amount of a therapeutic agent that causes the therapeutic effect to the amount that causes death (in animal studies) or toxicity (in human studies).
Therapeutic index

\[
\text{Therapeutic index} = \frac{\text{TD}_{50}}{\text{ED}_{50}}
\]
PK-PD changes in critical illness

- Circulatory failure
- Hepatic failure
- Renal failure
- Systemic Inflammatory Response Syndrome
- Changes in receptors in acute illness
- Protein binding
PK-PD changes in critical illness

Circulatory failure

• A greater percentage of cardiac output will go to essential organs (heart and brain)
  – Increased drug concentration in Heart and Brain
  – Decreased drug concentration in periphery
  – Decreased renal blood flow
  – Decreased liver blood flow

• Mechanical ventilation may further decrease liver blood flow due to increased intra thoracic pressure
PK-PD changes in critical illness

Hepatic failure

• High extraction vs low extraction drugs
• Loading doses not greatly affected
• Poor correlation between conventional tests of liver function and the degree of impairment of drug metabolism
  – Vary widely over short periods
• Hepatic failure tends to decrease the amount of drug bound on protein because of accumulation of metabolites which compete for binding sites (high vs low protein binding?)
PK-PD changes in critical illness
Renal Failure

- Decrease in renal drug clearance
  - Glomerular function more (aminoglycosides)
  - Tubular function less (penicillines)
- Increase in volume of Distribution (Fluid retention)
- Decreased excretion of liver metabolized drugs; Accumulation of active metabolites
  - Morphine → Morphine-6-glucuronide
- Protein binding alters due to metabolic products (uremia)
- Renal Replacement Therapy
  - Mode
  - Membrane
  - Drug
PK-PD changes in critical illness

SIRS

• Increase in volume of distribution due to increased capillary permeability
  – Increased loading dose

• Can change over short periods of time due to recovery
  – Check drug levels (vancomycin)
PK-PD changes in critical illness
Changes in receptors in acute illness

• Catecholamines
  – Up/down-regulation in absence/presence of agonist
  – pH dependent (pH < 7.1)
  – Temp dependent

• Suxamethonium
  – Extrajunctional Acetylcholine receptors on muscle after acute injuries (Burns/Denervation)
  → Hyperkalaemia
PK-PD changes in critical illness
Protein binding

- Acid drugs bind to albumin
- Basic drugs to $\alpha_1$ - acid glycoprotein
- Lipophilic drugs to Lipoproteins

- If the free concentration determines drug effect and drug clearance, the net effect is negligible
- Midazolam in renal failure
  - Despite increased clearance
  - Proteinbinding down $\Rightarrow$ Increased effect
- Propofol
  - Free propofol concentration increases $\Rightarrow$ Increased effect
PK-PD and ...

• Sepsis - Antibiotics
• Sedatives / Analgesia
• Catecholamines
• .....
PK-PD and Sepsis / Antibiotics

- In Sepsis and Septic Shock, early and appropriate antimicrobial therapy has been shown to be the predominant factor for reducing mortality.
- SEPSIS = SIRS + INFECTION
Sepsis = the systemic response to infection, manifested by two or more of the following conditions as a result of infection: (1) temperature $>38^\circ\text{C}$ or $<36^\circ\text{C}$; (2) heart rate $>90$ beats per minute; (3) respiratory rate $>20$ breaths per minute or $\text{PaCO}_2 < 32 \text{ mm Hg}$; and white blood cell count $>12,000/\text{cu mm}$, $<4,000/\text{cu mm}$, or $>10\%$ immature (band) forms.

Severe sepsis = sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Hypoperfusion and perfusion abnormalities may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status.

Septic shock = sepsis-induced with hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities that may include, but are not limited to, lactic acidosis, oliguria, or an acute alteration in mental status. Patients who are receiving inotropic or vasopressor agents may not be hypotensive at the time that perfusion abnormalities are measured.

Sepsis-induced hypotension = a systolic blood pressure $<90 \text{ mm Hg}$ or a reduction of $\geq 40 \text{ mm Hg}$ from baseline in the absence of other causes for hypotension.
Sepsis and changes in Vd

• Fluid shifts
  – Capillary leak
    • Endotoxines / exotoxines
  – Resuscitation
    • Shock is fluid
  – **Increase Vd for hydrophylic antimicrobials**
  – **Unchanged Vd for Lipohilic antimicrobials**

• Tissue perfusion/Tissue Penetration and Target side Distribution
• Protein binding
Sepsis and changes in Vd

- Fluid Shifts
- Tissue perfusion/Tissue Penetration and Target side Distribution
  - Plasma concentration ≠ tissue concentration
    - Capillary leakage
    - Oedema
    - Microvascular failure
  - Higher plasma concentrations to achieve the target concentration
  - Microdialysis
  - Example: Bacterial meningitis
- Protein binding
Microdialysis

• Measurement of interstitial concentrations
• sampling of analytes from the interstitial space by means of a semipermeable membrane at the tip of a microdialysis probe
  – skeletal muscle
  – Subcutaneous adipose tissue
The present study shows that piperacillin concentrations in the interstitium of soft tissues were five- to ten-fold lower than corresponding free plasma concentrations after a single intravenous dosage of 4 g in septic shock patients.

The special case of the brain

• Drug penetration in the brain is limited by passive and active defence mechanisms =BBB or blood brain barrier
  – Tight junctions of endothelial cells
  – Efflux pumps
• Altered with damaged BBB
  – meningitis
Sepsis and changes in Vd

- Fluid shifts
- Tissue perfusion/Tissue Penetration and Target side Distribution
- Protein binding
  - Most important albumine.
    - Decreased synthesis
    -Leaks extracapillary
- Unbound fraction
  - Active
  - Redistributes
  - Cleared
Sepsis and changes in Clearance

• Increased cardiac output and increased Clearance
  – Hyperdynamic state
  – Fluid and inotrope resuscitation
  – hydrophilic medication / Unbound fractions
• End-Organ dysfunction and decreased Clearance
  – Renal failure
  – Hepatic failure
    → Accumulation of drugs and/or metabolites
• Renal Replacement Therapy
  – Modality dependent
• ECMO
  – Increase Vd
  – Binding of drugs to the circuit
• Plasma exchange
  – Drugs with low Vd and high protein binding are lost
Sepsis and changes in metabolism

• Hepatic metabolism of drugs with a high extraction ratio:
  – Blood flow dependent

• Hepatic metabolism of drugs with a low extraction ratio:
  – Unbound fraction dependent
  – Activity hepatic enzymes
  – Clindamycin binds to $\alpha_1$ - acid glycoprotein (a positive acute phase protein) -> less clearance
Sepsis an changes in absorption

- Prefered IV
- Discussed before
Figure 3. Schematic representation of the basic pathophysiologic changes that can occur during sepsis and their subsequent pharmacokinetic effects. Note that there can be significant overlap between the groups above enabling multiple permutations for altered drug pharmacokinetics, e.g. patients with mild-to-moderate renal failure may develop increased transintestinal clearance of ciprofloxacin resulting in relatively normal plasma concentrations (39). CL, clearance; Vd, volume of distribution.
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<tr>
<th></th>
<th>General PK</th>
<th>Altered PK in Critically Ill</th>
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<tbody>
<tr>
<td><strong>Hydrophilic antibiotics</strong></td>
<td>Low</td>
<td>$V_d$</td>
</tr>
<tr>
<td></td>
<td>Predominantly renal</td>
<td>$ CL $</td>
</tr>
<tr>
<td></td>
<td>Poor intracellular penetration</td>
<td>Distribution</td>
</tr>
<tr>
<td></td>
<td>Examples: Beta-lactams, carbapenems, aminoglycosides, glycopeptides, linezolid</td>
<td>$\uparrow V_d$ depending on renal function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>$\downarrow$ Interstitial penetration</td>
</tr>
<tr>
<td><strong>Lipophilic antibiotics</strong></td>
<td>High</td>
<td>$V_d$</td>
</tr>
<tr>
<td></td>
<td>Predominantly hepatic</td>
<td>$ CL $</td>
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<td></td>
<td>Good intracellular penetration</td>
<td>Distribution</td>
</tr>
<tr>
<td></td>
<td>Examples: fluoroquinolones, macrolides, tigecycline, lincosamides</td>
<td>$\uparrow$ or $\downarrow$ depending on hepatic function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unchanged interstitial penetration</td>
</tr>
</tbody>
</table>
Kill characteristics of antibiotics

- Time dependent
- Concentration dependent
- Concentration dependent with time dependence
Figure 1. Pharmacokinetic and pharmacodynamic parameters of antibiotics on a concentration vs. time curve. Key: $T > MIC$—The time for which a drug’s plasma concentration remains above the minimum inhibitory concentration (MIC) for a dosing period; $C_{\text{max}}$/MIC, the ratio of the maximum plasma antibiotic concentration ($C_{\text{max}}$) to MIC; $AUC$/MIC, the ratio of the area under the concentration time curve during a 24-hour time period ($AUC_{0-24}$) to MIC.
Fig. 2. Flow diagram summarizing the effects of pathophysiologic changes on PK/PD parameters of hydrophilic antibiotics. AUC, area under the curve; $C_{\text{max}}$, maximum drug concentration; $C_{\text{min}}$, minimum drug concentration; CL, clearance; CO, cardiac output; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; $V_d$, volume of distribution.
**Fig. 3.** Flow diagram summarizing the effects of pathophysiologic changes on PK/PD parameters of lipophilic antibiotics. AUC, area under the curve; $C_{\text{max}}$, maximum drug concentration; $C_{\text{min}}$, minimum drug concentration; CL, clearance; CO, cardiac output; MIC, minimum inhibitory concentration; PK/PD, pharmacokinetic/pharmacodynamic; $V_d$, volume of distribution.
References