Time Course of Drug Action

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Introduction to Pharmacokinetics I

Drug effects are proportional to the level of drug in the plasma.
Drug in plasma is in equilibrium with drug at action site.
The time course of drug action is a function of input (absorption, distribution into blood from tissue, enterohepatic cycling) and output processes (distribution out of blood into tissue, metabolism, excretion).

Introduction to Pharmacokinetics II

Changes in pharmacokinetics will alter drug effects.
Patient characteristics such as age, tissue function, living habits and nutrition will alter the pharmacokinetics of drugs.
Drug dose, dose interval or both must be altered to compensate for changes in drug pharmacokinetics.

Blood-Drug Concentration Time Curve

Drug effect is proportional to level of drug in plasma.

Chemical equivalence ≠ therapeutic equivalence

Excipients (taste, solubility, bulk)
Chemical form (salt, free acid, ester)
Disintegration and dissolution characteristics

Zero-Order Kinetics I

Saturable Processes: Enzymes and Transport Carriers
Constant Rate (zero-order) at saturation.
Rate independent of drug concentration at saturation.
Absorption: iv drip and iv infusion
implantation pellet
anesthetic gases
sustained release reparations
Zero-Order Kinetics II

Elimination curve for zero-order kinetics

Zero order elimination lowers drug level at constant rate which is independent of the level of drug.

Alcohol elimination

Rate of elimination of alcohol is constant, independent of concentration

One drink eliminated per hour (constant amount)

Input > output = ethanol accumulates (2-3 drinks accumulated = 0.1% ethanol)

Input = output (1 drink per hour) no accumulation

clear 1 drink/h (constant)
input > 1 drink/h (drunk)
input = 1 drink/h (constant)
Input < 1 drink/h (sober)

First-Order Kinetics

Exponential Decline
Common Process
Changing Rate
Rate proportional to drug Concentration.
50% every t ½

First-Order Kinetic Equations I

Half-life [t ½] = 0.693 / ke **

ke = first-order elimination rate constant
time to eliminate 50% of drug

Ke = Clearance / Vd **
Clearance (total body)
Vd (volume of distribution)
t ½ = [0.693][Vd] / Clearance

First-Order Kinetic Equations II

Vd = Q/Co **
Q = drug dose
Co = plasma drug concentration at time zero

Clearance = [ke][Vd]
Clearance = [0.693][Vd] / t ½
Vd = Clearance / ke

First-Order Kinetic Equations III

Ke = 0.693 / t ½
Co = Q/Vd
Q = |Co|Vd

Be able to calculate:
Vd, t ½, Clearance, ke, Co and Q
Drug Accumulation (Zero-Order elimination)

Drug given at a constant rate (repeated dose).
Phenytoin cleared by liver.
Elimination rate constant at high doses.
Saturation of liver enzymes.
Input > output = increase
Input = output = plateau
Does not plateau at all doses.

Drug Accumulation (First-Order elimination)

Drug given at a constant rate (repeated dose)
Digoxin is cleared by kidney.
Elimination rate (output) proportional to drug levels.
Does not saturate at high levels.
50% eliminated in each \( t_{\frac{1}{2}} \) interval.
Levels rise until input = output.
Plateau at all doses (7 \( t_{\frac{1}{2}} \)).

First-Order Elimination Time Course

<table>
<thead>
<tr>
<th>( t_{\frac{1}{2}} ) intervals</th>
<th>Amount of Drug (mg)</th>
<th>Dose</th>
<th>Drug's ( t_{\frac{1}{2}} ) = 4 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>50</td>
<td>Dose = 100 mg iv</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>75</td>
<td>94% of drug cleared at 4 ( t_{\frac{1}{2}} ).</td>
</tr>
<tr>
<td>3</td>
<td>12.5</td>
<td>87.5</td>
<td>To accumulate dose interval must be less than 4 ( t_{\frac{1}{2}} ).</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>94***</td>
<td>It takes 7 ( t_{\frac{1}{2}} ) to clear most of the drug.</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>97</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>98.5</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>0.75</td>
<td>99.3</td>
<td></td>
</tr>
</tbody>
</table>

Plateau Principle [First-Order elimination]

Dosing interval

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>A</th>
<th>B</th>
<th>A</th>
<th>B</th>
<th>A</th>
<th>B</th>
<th>A</th>
<th>B</th>
<th>A</th>
<th>B</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1g [Body]</td>
<td>1.5</td>
<td>1.5</td>
<td>.75</td>
<td>.75</td>
<td>1.75</td>
<td>.88</td>
<td>.94</td>
<td>.97</td>
<td>.99</td>
<td>1.0</td>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2g [Body]</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>1.5</td>
<td>3.5</td>
<td>1.75</td>
<td>3.75</td>
<td>1.88</td>
<td>3.88</td>
<td>1.94</td>
<td>3.94</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>

T \( t_{\frac{1}{2}} \) = 4 h  Dose Interval = 4  A = level of drug immediately after dose.
B = level of drug just before dose is give and drug cleared in each \( t_{\frac{1}{2}} \).
Drug accumulates until input = output (7 \( t_{\frac{1}{2}} \) = plateau [all doses].
Time course of plateau is determined by drug’s \( t_{\frac{1}{2}} \).
Loading dose (2g or 4g) then 1/2 at \( t_{\frac{1}{2}} \) interval.

Changes in plateau magnitude.

Alterations in Plateau Time Course

The plateau time course is a function of the drug’s \( t_{\frac{1}{2}} \).
\( t_{\frac{1}{2}} = 0.693 / ke \) (altered by excretion)
Increased excretion = decreased \( t_{\frac{1}{2}} \) and time course.
Decreased excretion = increased \( t_{\frac{1}{2}} \) and time course.
Loading Dose and then \( \frac{1}{2} LD \) at \( t_{\frac{1}{2}} \) intervals produces rapid plateau.
Not altered by one change in dose or dose interval.
Alterations in Magnitude of Plateau

Proportional to changes in drug dose.
Inversely proportional to changes in dose interval.
Inversely proportional to changes in drug clearance (t½).

Application of Pharmacokinetic Principles

\[ \text{Css} = \frac{F \times D}{K_e \times V_d \times T} \]

- \( \text{Css} \) = steady-state (plateau) level of drug in plasma
- \( F \) = bioavailability
- \( D \) = dose administered (mg or g) iv
- \( K_e \) = first-order elimination rate constant (1/min, h)
- \( V_d \) = volume of distribution (L)
- Clearance (CL) = \( K_e \times V_d \) (ml/min, L/h)

Pharmacokinetics of Theophylline I

Patient is a 70 kg male.
- \( F = 1 \)
- \( D = 370 \text{ mg} \)
- \( \text{CL} = 2.7 \text{ L/h} \)
- \( T = 9 \text{ h} \)
- \( V_d = 35 \text{ L} \)
- \( k_e = 0.08 \text{ h}^{-1} \)
- \( t\frac{1}{2} = 9 \text{ h} \)
- \( \text{MEC} = 10 \text{ mg/L} \)
- \( \text{MTC} = 20 \text{ mg/L} \)

\[ \text{Css} = \frac{F \times D}{\text{CL} \times T} = \frac{[1] \times 370 \text{ mg}}{2.7 \text{ L/h} \times 9 \text{ h}} = 15 \text{ mg/L} \]

\[ \text{Loading Dose} = \frac{V_d \times \text{Css}}{F} = \frac{35 \text{ L} \times 15 \text{ mg/L}}{1} = 525 \text{ mg} \]

Pharmacokinetics of Theophylline II

Maintenance Dose = \( \frac{\text{Css} \times \text{CL} \times T}{F} \)

\[ = \frac{[15 \text{ mg/L}] \times [2.73 \text{ L/h}] \times [9 \text{ h}]}{1} = 370 \text{ mg} \]

\( t\frac{1}{2} = 0.693 / k_e = 0.693 / .08 \text{ h}^{-1} = 9 \text{ h} \)

\( \text{CL} = 0.693 \times V_d \times t\frac{1}{2} = [0.693] \times [35 \text{ L}] / 9 \text{ h} = 2.70 \text{ L} \)

\( V_d = t\frac{1}{2} \times \text{CL} / 0.693 = [9 \text{ h}] \times [2.7 \text{ L/h}] / 0.693 = 35 \text{ L} \)

Pharmacokinetic Problems I

Principle: It takes 1, 2, 3, 4, 5, 6 and 7 \( t\frac{1}{2} \) s to clear and accumulate 50, 75, 88, 94, 97, 99, and 100% of drug.

When will a drug with a \( t\frac{1}{2} \) of 8 h reach 75% ofCss if given every 4 h?
What if drug is given every 12 h?
Which situation gives the highest Css level?
Pharmacokinetic Problems II

Principle: It takes 1, 2, 3, 4, 5, 6 and 7 t½ s to clear and accumulate 50, 75, 88, 94, 97, 99 and 100 % of drug.

A drug was given iv and 24 h later 94% of the drug was excreted. What is the t½ of this drug?

Pharmacokinetic Problems III

Principle: It takes 1, 2, 3, 4, 5, 6 and 7 t½ s to clear and accumulate 50, 75, 88, 94, 97, 99 and 100 % of drug.

How long will it take to eliminate 750 mg of a 1000 mg iv dose, if this drug has a t½ of 6 h?

Pharmacokinetic Problems IV

Principle: It takes 1, 2, 3, 4, 5, 6 and 7 t½ s to clear and accumulate 50, 75, 88, 94, 97, 99 and 100 % of drug.

What is the t½ of a drug if 940 mg of a 1000 mg iv dose is eliminated in 24 h?

Pharmacokinetic Problem V

What is the Css of a drug that is 100% bioavailable (F = 1), when 250 mg of this drug is administered iv every 10 h to a Patient that clears this drug at a rate of 2.5 L/h?

\[ \text{Css} = \frac{F \times D}{CL \times T} = \frac{1 \times 250 \text{ mg}}{2.5 \text{ L/h} \times 10 \text{ h}} = 10 \text{ mg/L} \]