Time Course of Drug Action

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Introduction to Pharmacokinetics

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 drug absorption, distribution, metabolism and excretion (pharmacokinetics).

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.

Determining Drug Efficacy

Three Brands of Drug
Altered Bioavailability
2 is good 1&3 are not
MTC: [toxic level]
MEC: [effective level]

Zero-Order Reaction 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 reparrations
**Zero-Order Reaction Kinetics II**

iv infusion lowers drug level at constant rate which is independent of the level of drug.

**Metabolism of Alcohol**

**Alcohol**

↓ Alcohol Dehydrogenase (slow)

**Acetaldehyde (toxic)**

↓ Acetaldehyde Dehydrogenase (fast)

**Acetate**

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

**First-Order Reaction Kinetics**

Exponential Decline

Common Process

Changing Rate

Rate proportional to drug Concentration.

50% every t ½

**First-Order Kinetic Equations I**

Half-life \( t \frac{1}{2} \) = \( 0.693 / k_e \)

\( k_e \) = first-order elimination rate constant

time to eliminate 50% of drug

\( K_e = \frac{\text{Clearance}}{\text{Vd}} \)

Clearance (total body)

\( \text{Vd} \) (volume of distribution)

\[ t \frac{1}{2} = \frac{0.693}{\text{Vd}} / \text{Clearance} \]

**First-Order Kinetic Equations II**

\( \text{Vd} = \frac{Q}{\text{Co}} \)

\( Q \) = drug dose

\( \text{Co} \) = plasma drug concentration at time zero

Clearance = \( k_e [\text{Vd}] \)

\( \text{Vd} = \frac{\text{Clearance}}{k_e} \)

**First-Order Kinetic Equations III**

\( K_e = 0.693 / t \frac{1}{2} \)

\( \text{Co} = \frac{Q}{\text{Vd}} \)

\( Q = [\text{Co}][\text{Vd}] \)

Be able to calculate:

\( \text{Vd}, t \frac{1}{2}, \text{Clearance}, k_e, \text{Co} \) and \( Q \)
Drug Accumulation (Zero-Order CL)
Phenytoin cleared by liver. CL is constant at high doses. Saturation of liver enzymes. Input > output = increase Input = output = plateau Does not plateau at all doses.

Drug Accumulation (First-Order CL)
Digoxin is cleared by kidney. Clearance is non-saturable. Clearance is dose-dependent. 50% in each t½ interval. Levels rise until input = output. Plateau at all doses (7 t½).

First-Order Elimination Time Course

<table>
<thead>
<tr>
<th>T ½ intervals</th>
<th>Amount of Drug (mg)</th>
<th>In Body</th>
<th>Eliminated</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>75</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>12.5</td>
<td>87.5</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>94***</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>97</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>1.5</td>
<td>98.5</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0.75</td>
<td>99.3</td>
<td>0</td>
</tr>
</tbody>
</table>

Drug’s t½ = 4 h
Dose = 100 mg iv
94% of drug cleared at 4 t½.
To accumulate dose interval must be less than 4 t½.
It takes 7 t½ to clear most of the drug.

Plateau Principle [First-Order CL]

Time course of plateau is determined by drug’s t½.
Loading dose (2g or 4g) then ½ at t½ interval

Changes in plateau magnitude.

Alterations in Plateau Time Course

The plateau time course is a function of the drug’s t½.
t½ = 0.693 / ke (altered by excretion)
Increased excretion = decreased t½ and time course.
Decreased excretion = increased t½ and time course.
Loading Dose and then ½ LD at t½ 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 ($t\frac{1}{2}$).

Application of Pharmacokinetic Principles

\[ \text{Css} = \frac{F \times D}{ke \times Vd \times T} \]

- \( \text{Css} \): steady-state (plateau) level of drug in plasma
- \( F \): bioavailability
- \( D \): dose administered (mg or g) iv
- \( ke \): first-order elimination rate constant (1/\text{min, h})
- \( Vd \): volume of distribution (L)
- \( T \): dose interval (h)

Pharmacokinetics of Theophylline I

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

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

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

Pharmacokinetics of Theophylline II

- \( F = 1 \)
- \( D = 370 \text{ mg} \)
- \( CL = 2.7 \text{ L/h} \)
- \( t\frac{1}{2} = 9 \text{ h} \)
- \( \text{MEC} = 10 \text{ mg/L} \)
- \( \text{MTC} = 20 \text{ mg/L} \)

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

\[ t\frac{1}{2} = 0.693 / ke = 0.693 / 0.08 \text{ h}^{-1} = 9 \text{ h} \]

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

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

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% of Css 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 1/2 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 t 1/2 of this drug?

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Pharmacokinetic Problems III

Principle: It takes 1, 2, 3, 4, 5, 6, and 7 1/2 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 t 1/2 of 6 h?

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Pharmacokinetic Problems IV

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

What is the t 1/2 of a drug if 940 mg of a 1000 mg iv dose is eliminated in 24 h?

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Pharmacokinetic Problem V

What is theCss 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?

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