Mechanisms of Drug Action I

The method of expressing agonist and antagonist dose-response relationships that produce straight lines [a], hyperbolic curves [b], and S-shaped curves [c]

- Lineweaver-Burke
- Michaelis-Menten
- Log Dose-Response
- Law of Mass Action
- Occupancy Theory of Drug Action

Mechanisms of Drug Action II

- Lineweaver-Burke
- Michaelis-Menten

Mechanisms of Drug Action III

- Competitive Inhibitor
- Non-Competitive Inhibitor

Mechanisms of Drug Action IV

A patient ingests an agent that produces various dose-response curves. Curve A is the agonist alone, curve B is the agonist plus a low dose of the ingested agent, curve C is the agonist plus a moderate dose of the ingested agent and curve D is the agonist plus a high dose of the ingested agent. The ingested agent is:

- A competitive antagonist [Fig. 1] [higher $K_D$ & lower potency & affinity]
- A non-competitive antagonist [Fig. 2] [lower $E_{max}$ & lower efficacy]
- An irreversible antagonist (non-competitive) in the presence of spare receptors [Fig. 3]

Mechanisms of Drug Action V

- Competitive Inhibitor
- Non-Competitive Inhibitor

No spare receptors are present.
Mechanisms of Drug Action VI

An irreversible antagonist (non-competitive) in the presence of spare receptors.

Mechanisms of Drug Action VII

Select the statements that are not true about the effects of a competitive (IC) and a non-competitive (INC) antagonist on an agonist.

IC increases the agonist’s KD
IC decreases the agonist’s Emax ***
IC lowers the agonist’s affinity/potency
INC decreases the agonist’s Emax
INC lowers the agonist’s efficacy
INC increases the agonist’s KD ***
INC decreases the agonist’s KD ***

IC has the same Emax, higher KD [lower affinity & potency]
INC has the same KD, lower Emax [lower efficacy]

Mechanisms of Drug Action VIII

Select the processes that are not associated with receptor-mediated transmembrane signaling processes.

influx of extracellular calcium
activation of tyrosine kinase
increase in gene transcription
influx of extracellular sodium
activation of phospholipase C (DAG, IP3, calcium)
activation of adenylyl cyclase (c-CAMP)
activation of guanylyl cyclase (c-GMP)
activation of protein kinase
efflux of intracellular calcium ***
activation of phosphodiesterase ***

Mechanisms of Drug Action IX

In the Occupancy Theory of Drug Action an agonist has high ______ and an antagonist has high ______?

D + R K2 K1 [AFFINITY] K3 [EFFICACY] DR RESPONSE
K1,K2,K3 K1,K3
K1,K3 K2,K3
K2,K3 K1,K2
K1,K2,K3 K1 ***
K1,K2 K1,K3

Drug Absorption I

<table>
<thead>
<tr>
<th>pH</th>
<th>Weak Acids</th>
<th>% ionization of aspirin</th>
<th>Weak Bases</th>
<th>% ionization of codeine</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 units &gt; pKa</td>
<td>99.9% log [A/HA = 1000/1]</td>
<td>0.1% log [B/BH+ = 1000/1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 units &gt; pKa</td>
<td>99% log [A/HA = 100/1]</td>
<td>1% log [B/BH+ = 100/1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 unit &gt; pKa</td>
<td>98.9% log [A/HA = 10/1]</td>
<td>9% log [B/BH+ = 10/1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pH = pKa</td>
<td>50% log [A/HA = 1/1]</td>
<td>50% log [B/BH+ = 1/1]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 unit &lt; pKa</td>
<td>9% log [A/HA = 1/10]</td>
<td>98.9% log [B/BH+ = 1/10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 units &lt; pKa</td>
<td>1% log [A/HA = 1/100]</td>
<td>99% log [B/BH+ = 1/100]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 units &lt; pKa</td>
<td>0.1% log [A/HA = 1/1000]</td>
<td>99.9% log [B/BH+ = 1/1000]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Drug Absorption II

What percent of a weak base (pKa = 7.5) and weak acid (pKa = 3.5) will be respectively ionized in urine of pH 5.5?

1% and 1% pH – pKa = log Base/Acid
9% and 91% [Acid] 5.5 – 3.5 = 2 log 100 = 2 A / HA = 100/1
50% and 50% [Base] 5.5 - 7.5 = -2 log .01 = -2 B / BH+ = 1/100
91% and 9% 99% and 99% ***
**Drug Absorption III**

Select the route of administration that will produce the slowest onset of drug action [1], most rapid onset of action [2] and a first-pass liver effect [3].

- Oral [3]
- Intravenous [2]
- Rectal [1]
- Intramuscular
- Subcutaneous

**Drug Absorption IV**

Select the statements that are not true about the advantages and disadvantages of parenteral and enteral routes of drug administration.

**Enteral advantages:**
- Safe, economical, high bioavailability***
- Rapid onset of action***

**Enteral disadvantages:**
- Slow onset of action, low bioavailability,
- First pass liver effect, patient compliance***

**Parenteral advantages:**
- High bioavailability, fast onset of action,
- Patient compliance, safe***, economical***

**Parenteral disadvantages:**
- Expensive, more dangerous, patient compliance***, first pass liver effect***

**Drug Absorption V**

Select the mechanism by which small water soluble agents [1], most lipophilic drugs [2] and large molecular weight hormones [3] cross membranes.

- Filtration [1]
- Active transport
- Facilitated transport
- Passive diffusion [2] [major mechanism]
- Receptor mediated endocytosis [3]

**Drug Absorption VI**

Which of the following statements is not true about sublingual drug administration?

- By-pass portal circulation
- Rapid onset of drug action
- Excellent method of administering nitroglycerin and epinephrine
- Good method for administering many drugs***
- Difficult to hold drugs here for significant periods of time

**Drug Distribution I**

Select the body water compartments that represent 60%, 40%, 20%, 16% and 4% of an individual's total body weight.

- Total body water [60%]
- Extracellular water [20%] \( V_d = Q/C_p \)
- Intracellular water [40%]
- Plasma water [4%]
- Interstitial water [16%]

**Drug Distribution II**

Thiopental has a has a ______ duration of action because this agent is ______.

- Short rapidly excreted
- Long slowly excreted
- Long slowly metabolized
- Short rapidly redistributed***
- Short rapidly metabolized
- Short slowly redistributed
- Long slowly redistributed
Drug Distribution III
Phenobarbital poisoning is treated with ___ to ___ the extracellular pH and increase the clearance of phenobarbital.

- ammonium chloride: decrease
- ammonium chloride: increase
- sodium bicarbonate: increase ***
- sodium bicarbonate: decrease
- sodium hydroxide: decrease

Drug Distribution IV
The distribution of drugs to the brain is limited as a result of ___.

- blood-brain barrier ***
- blood-CSF barrier ***
- blood-extracellular barrier
- brain-CSF barrier ***
- blood-intracellular barrier

Drug Distribution V
Select the agent that can produce fetal abortion [1], malformation [2], retardation [3], withdrawal [4] and vaginal cancer later in life [5].
- cocaine [1,4]
- ethanol [3]
- thalidomide [2]
- morphine [4]
- diethylstilbesterol [5]

Drug Metabolism I
Which of the following statements is not true about the interaction between chronic alcohol intake and acetaminophen.

- Alcohol induces the hepatic metabolism of acetaminophen.
- Alcohol potentiates the hepatotoxicity of acetaminophen.
- Therapeutic levels of acetaminophen can produce liver damage in alcoholics.
- Liver damage can be reduced with the administration of n-acetylcycteine.
- The combination of alcohol and acetaminophen is not toxic in most alcoholics. ***

Drug Metabolism II
All of the following drugs or conditions induce drug metabolism except ____?
- phenobarbital
- smoking
- chronic alcohol intake
- phenytoin
- cimetidine ***
- rifampin
- chloramphenicol ***
Drug Metabolism III
All of the following drugs or conditions inhibit drug metabolism except?
- aging
- liver disease
- cimetidine
- chloramphenical
- acute alcohol intake
- charcoal broiled food ***
- testosterone ***
- newborn

Drug Metabolism IV
From the list below select an agent that produces liver injury in slow acetylators [1] and one that produces respiratory depression in patients with decreased plasma cholinesterase activity [2].
- isoniazid [1]
- chloramphenicol
- cimetidine
- succinylcholine [2]
- aspirin
- phenobarbital

Drug Metabolism V
Select the P450 induced by ethanol [1], smoking [2], phenobarbital [3,4], isoniazid [1] and rifampin [3,4].
- 2EI [1]
- 1A2 [2]
- 2B6 [3]
- 3A4 [4]

Drug Metabolism VI
Select the one agent that is not found in the urine after the administration of aspirin.
- salicylic acid
- salicyluric acid
- ether glucuronide of salicylic acid
- ester glucuronide of salicylic acid
- salicylacetic acid ***

Drug Excretion I
Drug clearance is decreased by all of the following except __?
- aging
- newborn
- liver disease
- kidney disease
- heart disease
- smoking ***
- phenobarbital ***

Drug Excretion II
Kidney function can be assessed by determining the glomerular filtration rate (GFR) and the renal plasma flow (RPF) by measuring the clearance of ____?
- creatinine and inulin
- para-aminohippuric acid (PAH) and probenecid
- inulin and PAH ***
- creatinine and probenecid
- inulin and probenecid
Drug Excretion III

When renal drug clearance is greater than [1], less than [2] and equal to [3] the GFR the drug is primarily _____ by the nephron.

- secreted [1]
- reabsorbed [2]
- filtered [3]
- filtered, secreted and reabsorbed

Drug Excretion IV

Which of the following drugs are readily cleared as they pass through the liver (first-pass effect)?

- Propranolol ***
- Lidocaine ***
- Morphine ***
- Tolbutamide
- Phenobarbital

Drug Excretion V

Select the agent that can be used to reduce the enterohepatic cycling of drugs.

- propranolol
- cholestyramine ***
- morphine
- steroids
- phenobarbital

Drug Excretion VI

Nitrous oxide has a ____ λ, a _____ duration of action and a ____ rate of clearance.

- high, long, low
- low, short, rapid ***
- high, short, rapid
- low, long, low
- high, long, high

Drug Excretion VII

Select the agents that would be useful in reducing the high plasma uric acid levels associated with gout.

- probenecid ***
- aspirin ***
- cimetidine
- phenobarbital
- sodium bicarbonate

Pharmacokinetics I

If a drug has a half-life of 6 hours how long will it take to clear 100% of this drug and how many doses given at half-life intervals will be needed to reach 94% of the C∞?

- 42 h 4 ***
- 30h 6
- 48 h 5
- 24 h 7
- 36h 3

1 t ½ (50), 2 t½ (75), 3 t½ (88), 4 t½ (94), 6 t½ (99), 7 t½(100)
**Pharmacokinetics II**

Select the incorrect formula.

- \( V_d = \frac{Q}{C_0} \)
- \( CL = ke \times V_d \)
- \( t_{1/2} = \frac{0.693}{ke} \)
- \( Css = \frac{[F \times D]}{[CL \times T]} \)
- \( V_d = \frac{0.693 \times t_{1/2}}{CL} \)
- \( LD = \frac{[V_d \times C_p]}{F} \)
- \( MD = \frac{[Css \times CL \times T]}{F} \)
- \( CL = \frac{0.693 \times V_d}{t_{1/2}} \)

**Pharmacokinetics III**

The time course of a drug’s plasma plateau (\(Css\)) is altered by all of the following factors except _____?

- liver disease
- kidney disease
- a loading dose followed by a maintenance dose at constant intervals
- induction of hepatic drug metabolism
- inhibition of hepatic drug metabolism
- change in dose interval ***
- change in dose level ***
- aging
- heart disease

**Pharmacokinetics IV**

The magnitude of a drug’s plasma plateau (\(Css\)) is altered by all of the following factors except _____?

- change in dose interval
- change in dose level
- change in drug clearance \(Css = F \times D\)
- change in drug bioavailability \(CL \times T\)
- liver disease
- kidney disease
- aging
- heart disease
- route of drug administration

**Pharmacokinetics V**

The dose of drug should be reduced in all of the following except _____?

- elderly patients
- infants
- liver disease
- kidney disease
- smokers ***
- alcoholics (without liver damage) ***

**Pharmacokinetics VI**

What drug dose must be given at half-life intervals to obtain a \(Css\) of 300 mg?

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>(Css) / 1.5 = dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>(Css) = dose</td>
</tr>
<tr>
<td>100</td>
<td>(Css) = dose</td>
</tr>
<tr>
<td>150</td>
<td>(Css) = dose</td>
</tr>
<tr>
<td>200 ***</td>
<td>(Css) = average between peak (400 mg) and minimum (200 mg) blood levels.</td>
</tr>
<tr>
<td>300</td>
<td>(Css) = average between peak (400 mg) and minimum (200 mg) blood levels.</td>
</tr>
</tbody>
</table>

[if dose interval is equal to drug's half-life]

**Pharmacokinetics VII**

The desired \(Css\) of drug X is 300 mg. Eight hours after administering a single 300 mg dose of drug X there is only 75 mg of drug X remaining in the patient. What loading dose (LD), maintenance dose (MD) and dose interval (DI) would you recommend to reach and maintain the 300 mg \(Css\) as quickly as possible?

<table>
<thead>
<tr>
<th>LD (mg)</th>
<th>MD (mg)</th>
<th>DI (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>400</td>
<td>200</td>
<td>4 h ***</td>
</tr>
<tr>
<td>600</td>
<td>300</td>
<td>4 h</td>
</tr>
<tr>
<td>300</td>
<td>300</td>
<td>8 h</td>
</tr>
<tr>
<td>400</td>
<td>200</td>
<td>8 h</td>
</tr>
<tr>
<td>600</td>
<td>300</td>
<td>8 h</td>
</tr>
</tbody>
</table>
Pharmacokinetics VIII

A 400 mg dose of drug X is administered to a 220 pound man. The peak plasma level (Cp) of drug X is 1 mg/L. The Vd of drug X is?

- 4 L
- 40 L
- 400 L *** Vd = Q / Cp = 400 mg / 1 mg/L = 400 L
- 25 L
- 250 L

Pharmacokinetics IX

The pharmacokinetic characteristics of drug X are:

- Bioavailability (oral): 1
- % urinary excretion: 100
- Clearance (L/h/Kg): 0.1 x 100 Kg = 10 L/h
- Volume of distribution (L/Kg): 1 x 100 Kg = 100 L
- MEC: 1 mg/L
- MTC: 5 mg/L

Target Css/Cp = 3 mg/L.

The patient that you are administering drug X to is a 220 pound male with normal kidney function. Answer the following 4 questions. [2.2 pounds = 1 Kg] 220 pounds = 100 Kg

Pharmacokinetics X

What would be an appropriate plasma target level (Css and Cp) for drug X?

- 1 mg/L
- 2 mg/L
- 3 mg/L ***
- 4 mg/L
- 5 mg/L

Pharmacokinetics XI

This drug is primarily cleared by the ___ and follows______ kinetics.

- kidney zero-order
- liver zero-order
- kidney first-order ***
- liver first-order
- liver and kidney mixed kinetics

Pharmacokinetics XII

Calculate a loading dose that would produce the appropriate Css.

- 100 mg LD = Vd x Cp = 100 L x 3 mg/L
- 200 mg
- 300 mg ***
- 400 mg
- 500 mg

Pharmacokinetics XIII

Calculate the 4 h maintenance dose that would maintain the appropriate Css.

- 60 mg MD = Css x CL x T = 3 mg/L x 10 L/h x 4 h
- 120 mg *** F = 1
- 80 mg
- 160 mg
- 200 mg
**Drug Interactions I**

The renal clearance of drugs that are weak acids and bases will be increased respectively by ____?  
- sodium bicarbonate and ammonium chloride***  
- ammonium chloride and sodium bicarbonate  
- amphetamine and aspirin  
- antacids and phenobarbital  
- aspirin and antacids  
- probenecid. and amphetamine

**Drug Interactions II**

The absorption of tetracyclines and quinolones is reduced by all of the following except ______?  
- antacids  
- milk  
- iron  
- sodium ***  
- magnesium

**Drug Interactions III**

If one wants to maintain a higher plasma level of drugs such as methotrexate or penicillin that are readily secreted by the kidney then one should administer which of the following agents?  
- aspirin ***  
- probenecid ***  
- atropine  
- cimetidine  
- chloramphenicol  
- phenobarbital

**Drug Interactions IV**

Bilirubin [kernicterus], tolbutamide [hypoglycemia] and dicumarol [hemorrhage] are readily displaced from plasma albumin by all of the agents listed below except ____?  
- aspirin  
- phenobarbital ***  
- sulfonamides  
- salicylates  
- cimetidine ***

**Drug Interactions V**

Which of the following statements are true about epinephrine?  
- prolongs the duration of action of local anesthetics ***  
- interacts with imipramine to increase blood *** pressure  
- increases capillary blood flow  
- decreases blood pressure  
- is a vasodilator