Pharmacology Review

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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]

a. Lineweaver-Burke

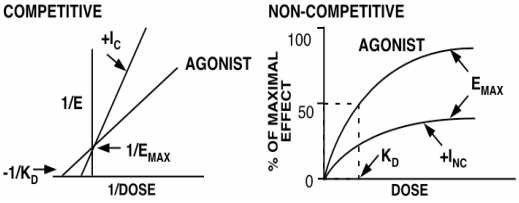
b. Michaelis-Menten

c. Log Dose-Response

d. Law of Mass Action

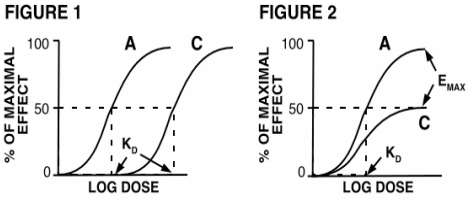
e. Occupancy Theory of Drug Action

Mechanisms of Drug Action II



Lineweaver-Burke **Michaelis-Menten**

Mechanisms of Drug Action III



Competitive Inhibitor **Non-Competitive Inhibitor**

Mechanisms of Action IV

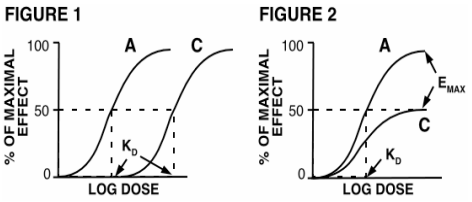
A patient ingests an agent that produces various dose-response curves. Curve A is the agonist alone, curve B is the agonist plus a low dose of the ingested agent, curve C is the agonist plus a moderate dose of the ingested agent and curve D is the agonist plus a high dose of the ingested agent. The ingested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

A competitive antagonist [Fig. 1] [higher K_D & lower potency & affinity]

A non-competitive antagonist [Fig. 2] [lower Emax & lower efficacy]

An irreversible antagonist (non-competitive) in the presence of spare receptors [Fig. 3]

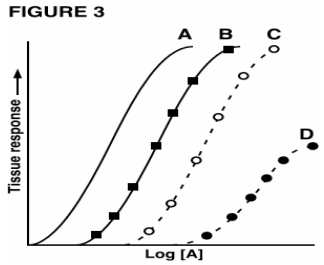
Mechanisms of Drug Action V



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 (I_C) and a non-competitive (I_{NC}) antagonist on an agonist.

I_C increases the agonist's K_D
I_C decreases the agonist's E_{max} ***
I_C lowers the agonist's affinity/potency
I_{NC} decreases the agonist's E_{max}
I_{NC} lowers the agonist's efficacy
I_{NC} increases the agonist's K_D ***
I_{NC} decreases the agonist's K_D ***

I_C has the same E_{max}, higher K_D [lower affinity & potency]

I_{NC} has the same K_D, lower E_{max} [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, IP_3, 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 $\overset{K2}{\leftarrow}$ $\overset{K1\ [AFFINITY]}{\rightarrow}$ DR $\overset{K3\ [EFFICACY]}{\rightarrow}$ 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

pH	Weak Acids % ionization of aspirin		Weak Bases % ionization of codeine	
3 units > pKa	99.9%	log [A^-/HA = 1000/1]	0.1%	log [B/BH^+ = 1000/1]
2 units > pKa	99%	log [A^-/HA = 100/1]	1%	log [B/BH^+ = 100/1]
1 unit > pKa	90.9%	log [A^-/HA = 10/1]	9%	log [B/BH^+ = 10/1]
pH = pKa	50%	log [A^-/HA = 1/1]	50%	log [B/BH^+ = 1/1]
1 unit < pKa	9%	log [A^-/HA = 1/10]	90.9%	log [B/BH^+ = 1/10]
2 units < pKa	1%	log [A^-/HA = 1/100]	99%	log [B/BH^+ = 1/100]
3 units < pKa	0.1%	log [A^-/HA = 1/1000]	99.9%	log [B/BH^+ = 1/1000]

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]

Intravascular [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%] Vd = Q/Cp

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

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.

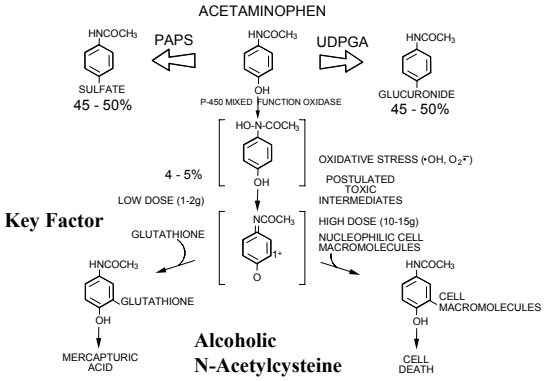
Alcohol potentiates the hepatotoxicity of acetaminophen.

Therapeutic levels of acetaminophen can produce liver damage in alcoholics.

Liver damage can be reduced with the administration of n-acetylcysteine.

The combination of alcohol and acetaminophen is not toxic in most alcoholics. ***

Acetaminophen Hepatotoxicity



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].

- **isonazid [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 salicylilc 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

pheobarbital

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_{SS}?

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.

- **Vd = Q / Co**
- **CL = ke × Vd**
- **$t^{1}/_{2}$ = .693 / ke**
- **Css = [F x D] / [CL × T]**
- **t ½ = [.693 × Vd] / CL**
- **CL = [.693 × $t^{1}/_{2}$] / Vd *****
- **LD = [Vd × Cp] / F**
- **MD = [Css × CL × T] / F**
- **CL = [.693 × Vd] / $t^{1}/_{2}$**

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 = $\frac{F \times D}{CL \times T}$**
- **change in drug bioavailability**
- **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?

- **50 mg** — **Css / 1.5 = dose**
- **100 mg**
- **150 mg** — **dose x 1.5 = Css**
- **200 mg *****
- **300 mg** — **Css = average between peak (400 mg) and minimum (200 mg) blood levels.**

[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?

LD	MD	DI
400 mg	200 mg	4 h ***
600 mg	300 mg	4 h
300 mg	300 mg	8 h
400 mg	200 mg	8 h
600 mg	300 mg	8 h

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 = 10L/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 = $\frac{Vd \times Cp}{F} = \frac{100\ L \times 3\ mg/L}{1}$**

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 = $\frac{Css \times CL \times T}{F} = \frac{3mg/L \times 10L/h \times 4\ h}{1}$**

120 mg *

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 [hemorrage] 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**