Review of Last Lecture

- Graded DRC
- Quantal DRC

Which parameters can measure from DRCs?

Affinity & Intrinsic activity

- Affinity: It is the ability of a drug to bind to the receptor (just bind)
- Intrinsic activity (or efficacy): It is the ability of a drug to activate a receptor following receptor occupation.

Efficacy and Potency

- Efficacy is the maximal response produced by a drug
- It depends on the number of drug-receptor complexes formed
- Potency is a measure of how much drug is required to elicit a given response
- The lower the dose required to elicit given response, the more potent the drug is

Potency

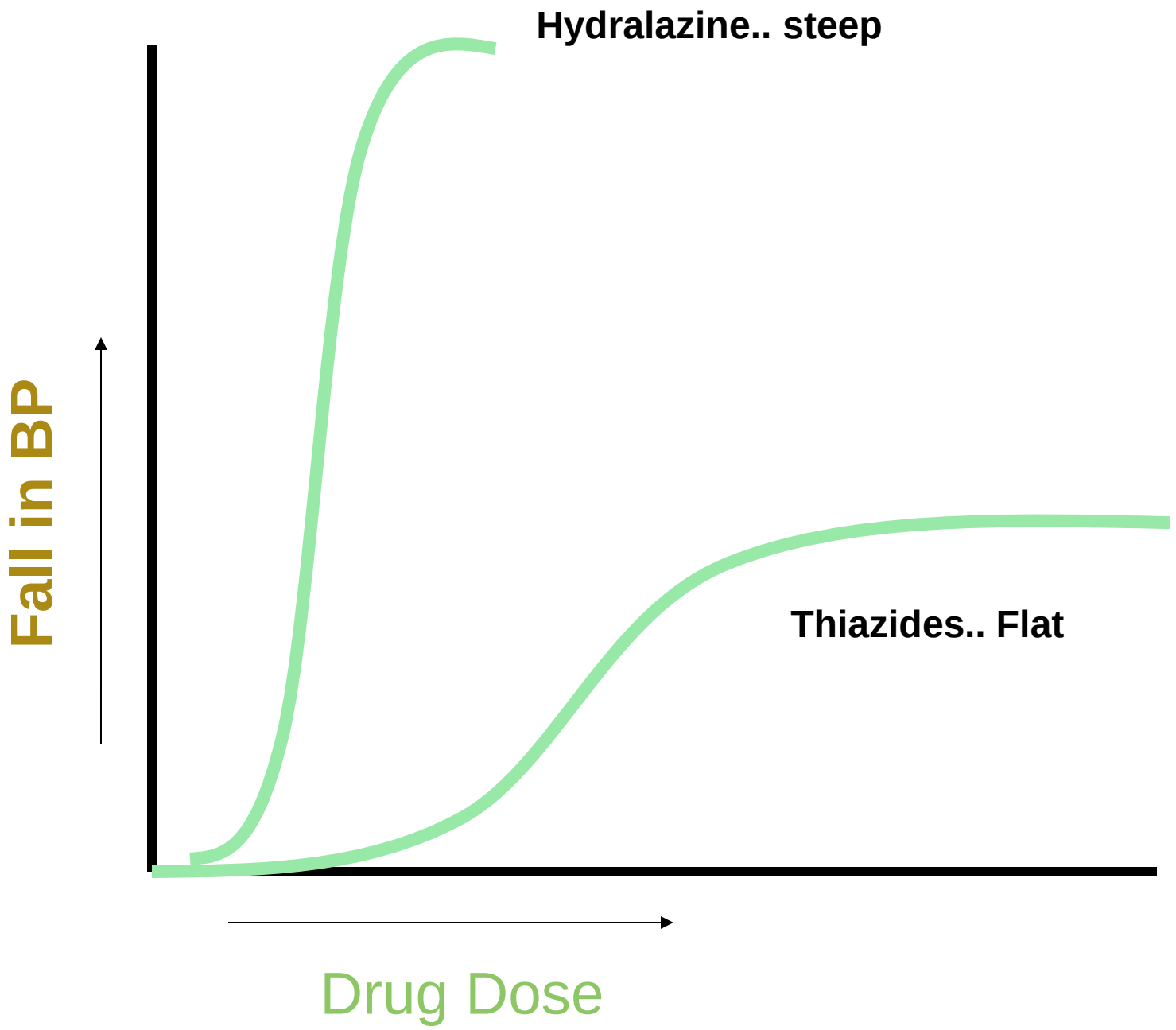
- Dose of a drug that required to produce 50% of maximal effect (**ED_{50} or EC_{50}**)
- Relative Positions of the DRC on x-axis
- More left the DRC, more potent the drug

Efficacy

- Maximum effect of the drug (E_{max})
- Height of the curve on y-axis indicates the efficacy of the drug
- Taller the DRC ,more efficacious the drug

Slope of DRC

- The slope of midportion of the DRC varies from drug to drug
- A steep slope indicates small increase in dose produces a large change in response


Hydralazine.. steep
Fall in BP
Thiazides.. Flat
Drug Dose

SLOPE

STEEP DRC

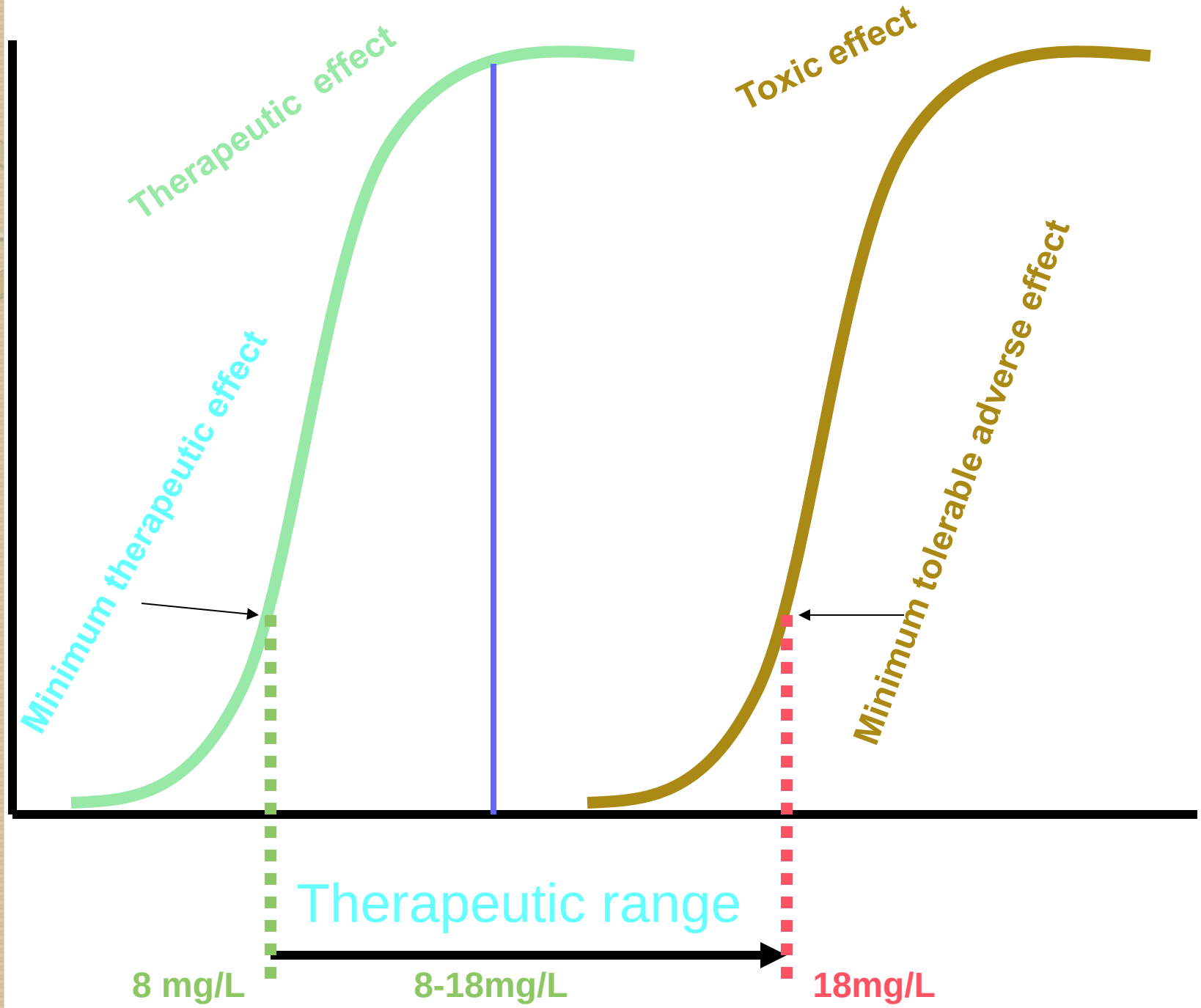
- Moderate increase in dose leads to more increase in response
- Dose **needs** individualization for different patients
- Unwanted and Uncommon

FLAT DRC

- Moderate increase in dose leads to little increase in response
- Dose ***needs no*** individualization for different patients
- Desired and Common

Therapeutic window

- It is a more clinically relevant index of safety
- It describes the dosage range between the minimum effective therapeutic concentration or dose, and the minimum toxic concentration or dose
- E.g. theophylline has an average minimum plasma conc of 8 mg/L and the toxic effects are observed at 18 mg/L
- The therapeutic window is 8 – 18 mg/L


EFFECT
Therapeutic effect
Toxic effect
Minimum therapeutic effect
Minimum tolerable adverse effect
Therapeutic range
8 mg/L
8-18mg/L
18mg/L

Clinical significance

- Drugs with a low TI should be used with caution and needs a periodic monitoring (less safe)
- E.g. warfarin, digoxin, theophylline
- Drugs with a large TI can be used relatively safely and does not need close monitoring (highly safe)
- E.g. penicillin, paracetamol
- Other terms used: wide safety margin, narrow safety margin

Competitive Vs Noncompetitive Antagonism

- COMPETITIVE
- Antagonist binds with same receptor site
- Chemical resemblance with agonist
- Parallel rightward shift of DRC
- Apparently reduces potency of agonist
- Intensity of response depends both on antagonist and agonist concentration
- Eg: Acetylcholine and Atropine

- NONCOMPETITIVE
- Same or Another site of receptor binding
- Does not resemble
- Flattening of DRC
- Apparently reduces efficacy of agonist
- Intensity of response depends mainly on antagonist concentration
- Eg: phenoxybenzamine (for pheochromocytoma)

Practice Question

- When tested under identical conditions with all statistical requirements rigidly applied, drug X has the following parameters: LD_{50}=0.5 mg/Kg

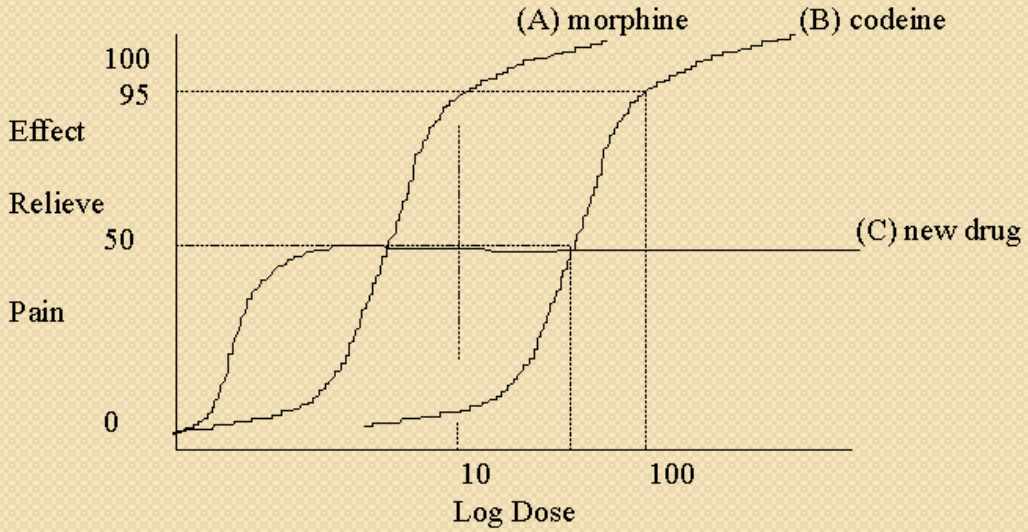
Ed_{50}=0.5 µg/Kg. The therapetic index is

1. 0.001
2. 0.1
3. 1.0
4. 10
5. 1000

Practice Question

- In the absence of other drugs, pindolol causes an increase in heart rate by activating beta adrenoceptors. In the presence of highly effective beta stimulants, however, pindolol causes a dose-dependent, reversible decrease in heart rate. Therefore, pindolol is probably
  - An irreversible antagonist
  - A physiologic antagonist
  - A chemical antagonist
  - A partial agonist
  - A spare receptor agonist

PRACTICE QUESTION



Which line is most efficacious?

Which is more potent?

Probing question

- A 55-year-old woman with congestive heart failure is to be treated with a diuretic drug. Drugs X and Y have the same mechanism of diuretic action. Drug X in a dose of 5 mg produces the same magnitude of diuresis as 500 mg of drug Y. This suggests that
  - Drug Y is less efficacious than drug X
  - Drug X is about 100 times more potent than drug Y
  - Toxicity of drug X is less than that of drug Y
  - Drug X is a safer drug than drug Y
  - Drug X will have a shorter duration of action than drug Y because less of drug X is present for a given effect

Therapeutic index is a measure of

(a) Safety

(b) Potency

(c) Efficacy

(d) Selectivity

True statement regarding inverse agonist is

(a) Binds to the receptor and causes intended action

(b) Binds to the receptor and causes opposite action

(c) Binds to the receptor and causes no action

(d) Binds to the receptor and causes submaximal action

All are reasons for alteration of drug dosage in the elderly EXCEPT

(a) They have decreasing renal function with age

(b) They are lean and their body mass is less

(c) Have increased baroreceptor sensitivity

(d) Body water is decreased

Regarding efficacy and potency of a drug, all are true

EXCEPT:

(a) In a clinical setup, efficacy is more important than

potency

(b) In the log dose response curve, the height of the

curve corresponds with efficacy

(c) ED50 of the drug corresponds to the efficacy

(d) Drugs that produce a similar pharmacological

effect can have different levels of efficacy

Which of the following terms best describes the

antagonism of leukotrienes' bronchoconstrictor

effect (mediated at the leukotriene receptors) by

terbutaline (acting at the adrenoceptors) in patient with asthma?

(a) Pharmacologic antagonist

(b) Partial agonist

(c) Physiologic antagonist

(d) Chemical antagonist

Which of the following terms best describes a drug
that blocks the action of adrenaline at its receptors
by occupying those receptors without activating
them?

(a) Pharmacologic antagonist
(b) Non competitive antagonist
(c) Physiologic antagonist
(d) Chemical antagonist

Mechanisms of Drug Action

1) Change the Physical and Chemical Properties of the cellular Environment:

Antacids neutralize gastric acid

IV mannitol induces diuretic effect (osmotic diuretic)

chelating agents (dimercaprol)

given to treat heavy metal poisoning, e.g lead, mercury, arsenic

2) Drugs exert their effects by receptor activation or inhibition

- **Agonists**
- **Antagonists**

3) Drugs exert their effects by modifying extracellular or intracellular enzymes which are responsible for physiologic processes.

Angiotensin Converting Enzyme inhibitors

Acetylcholinesteraz inhibitors

MAO inhibitors

COX inhibitors

Xantinoxidase inhibitors

HMG-CoA reductase inhibitors

4) Drugs exerts their effects as an antimetabolite

- Warfarin- antimetabolite of Vitamin K- impaire the synthesis of coagulation factors

- Metotreksat- antimetabolite of folic acid- impaire DNA synthesis

Co-enzymes and substrates of enzyme = metabolite

5) Drugs exert their effects by modulating active transmembranal transport systems

- Proton-pump inhibitors (Omeprazol) inhibit the gastric H^+- K^+ATPase to treat stomach ulcer
- Digital glycosides inhibit the Na^+-K^+ATPase of myocytes to increase their contractility

6) Drugs exert their effects by opening or closing transmembranal ion channels of excitable cells

- Local anaesthetics,
- Calcium channel blockers
- Some antiarrythmics

7) Replacement therapy

-Vitamin or hormone replacement

8) Drugs exert their effects by influencing physiological transmitters and hormones

Ephedrine enhances the release of NA from the adrenergic nerve endings.

Tolbutamide enhances the release of insulin and decreases the blood sugar concentration.

FACTORS MODIFYING DRUG ACTION

FACTORS INFLUENCING THE DRUG RESPONSE

DRUG FACTORS

PATIENT FACTORS

- Route of Drug Administration
- Presence of other drugs

DRUG FACTORS

1. Route of Drug Administration

Quantitative Variations

Oral dose of the drugs are usually larger than i.v. dose

e.g., i.v. dose of morphine is 5-10mg whereas oral dose is 30-60 mg for analgesic effect.

Qualitative Variations

The drug may produce an entirely different response when administered by different routes.

E.g., Magnesium sulfate orally produces purgative effect, parenterally it causes CNS depression and locally reduces oedema in inflamed area.

FACTORS INFLUENCING THE DRUG RESPONSE

DRUG FACTORS

PATIENT FACTORS

- **Physiological factors**

  Body weight, Age, Gender, pregnancy, lactation
- **Pathological factors**
- **Genetic factors**
- **Environmental factors and diet**

Patient factors
I. Physiological factors

Body size

- Body size can be a significant determinant of drug effects.
- Dosage must be adjusted to the size of the patient.

In general, drugs are given in the manner of mg or g per kg of body weight.

- An average dose of a drug is calculated in terms of body weight (mg/kg).

$$\text{Dose} = \frac{\text{Body Weight (kg)}}{70} \times \text{Average adult dose}$$

- In obese ,lean or in a patient with dehydration or oedema,
- In certain cases such as treatment with chemotherapeutics,

dose calculation on the basis of body weight is not very appropriate.

A more accurate method for calculating a dose is on the basis of the body surface area (BSA).

BSA takes account of not only BW but also how lean or fat a patient may be

I. Physiological factors

Age

- Extreme of age show extreme drug sensitivity
- Drug sensitivity ***in the very young*** and ***in the elderly*** results largely from ***organ system immaturity*** and ***organ system degenerations***, respectively
- Newborn babies & elderly= greater & more prolonged effect of drugs because of less efficient drug metabolism & renal functions

Newborn: Decreased

- ↓ gastric acid secretion.
- ↓ liver microsomal enzymes (glucuronyl transferase).
- ↓ Plasma protein binding.
- ↓ GFR & tubular secretion.
- Immaturity of BBB in neonates.

- **GIT absorption of ampicillin and amoxicillin is greater in neonates** due to decreased gastric acidity.

- **Chloramphenicol --- Grey baby syndrome**
  Inadequate glucouronidation of chloramphenicol with drug accumulation).

- **Sulfonamides ------ Hyperbilirubinemia & Kernicterus**

- **Tubular function is also diminished.**
  Normal plasma half life of gentamicin is 1-4 hrs,

  in babies it is 10 hrs and
  in premature babies it may be up to 18 hrs.

CHILDREN

- **Tetracyclines**

Permanent teeth staining

- **Corticosteroids**

Growth & development retardation

- **Antihistaminics**

Hyperactivity.

TABLE 11–1 • Physiologic Changes That Can Affect Pharmacokinetics in the Elderly

Absorption of Drugs
Increased gastric pH
Decreased absorptive surface area
Decreased splanchnic blood flow
Decreased GI motility
Delayed gastric emptying
Distribution of Drugs
Increased body fat
Decreased lean body mass
Decreased total body water
Decreased serum albumin
Decreased cardiac output
Metabolism of Drugs
Decreased hepatic blood flow
Decreased hepatic mass
Decreased activity of hepatic enzymes
Excretion of Drugs
Decreased renal blood flow
Decreased glomerular filtration rate
Decreased tubular secretion
Decreased number of nephrons

Old Age

– ↓ **Liver function.**

diazepam, theophylline.

– ↓ **Kidney function.**

Digoxin, lithium.

– ↓ **Plasma protein binding**

– ↑**sensitivity to CNS depressants**

diazepam, morphine

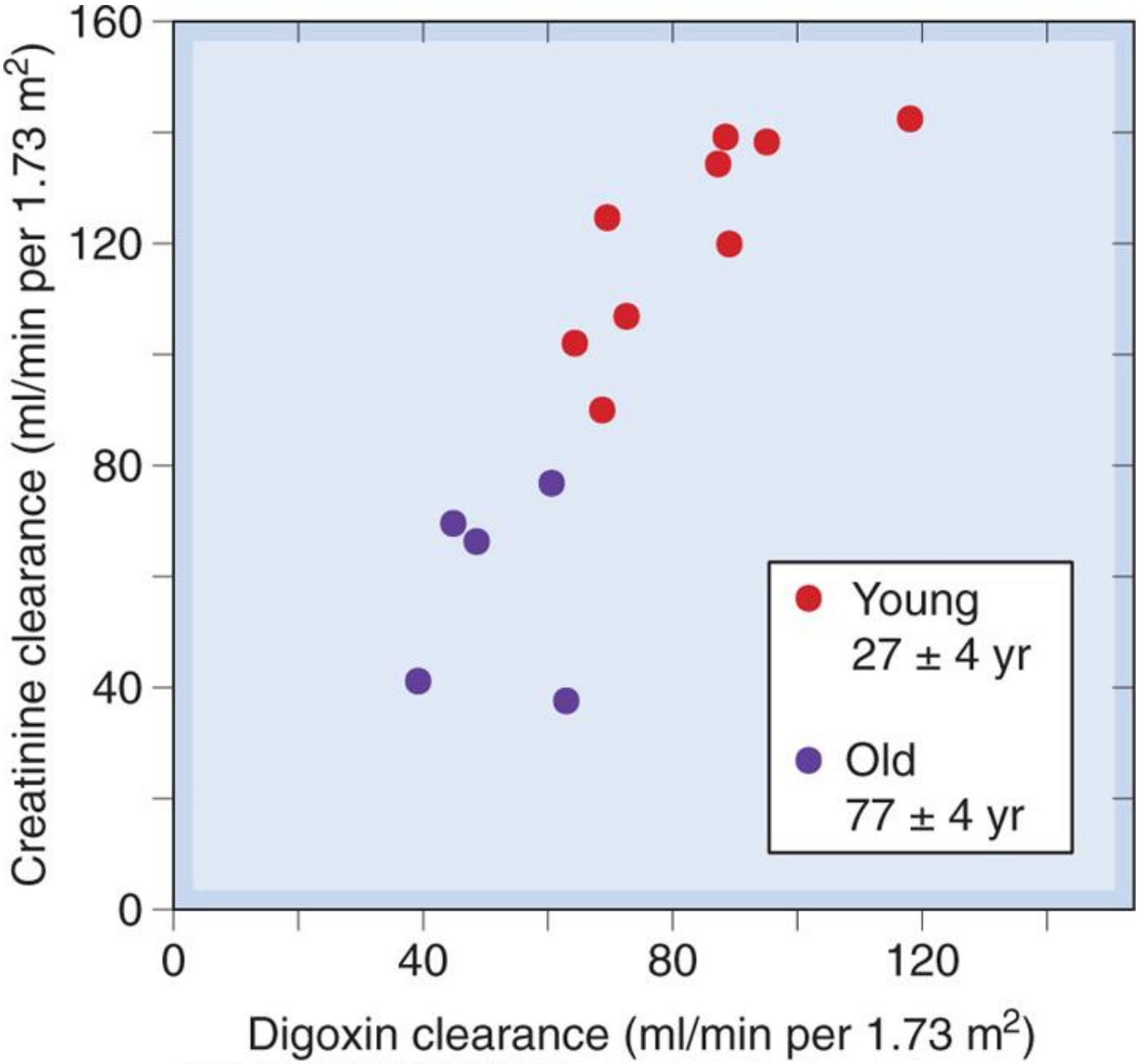
- Activity of hepati microsomal enzyme also decreases with ag leading prolonged hal life of some drugs.

This may lead t accumulation of drug o repeated doses.

- **there is a decrease in G.F.R with ages**

  G.F.R declines to 25% in person of 50 years of age and 50% in person 75 years of age.

- **Gentamycin ,Digoxin ,Pencillins are contraindicated in old people.**



- **Other factors effecting drug sensitivity in the elderly:**

✓ **increased severity of illness**

✓ **Presence of multiple pathologies**

✓ **treatment with multiple drugs**

✓ **poor adherence**

I. Physiological factors

Sex/Gender

- men and women may respond differently to the same drugs
- Metabolism of some drugs is less in women (more adipose tissues)

E.g., alcohol, diazepam

- Women require lesser dose than male

I. Physiological factors

Sex/Gender

- Famales are more susceptable to autonomic drugs (estrogen inhibits choline estrase)
- Testosteron increases rate of biotransformation of drugs.
- Aspirin shows greater benefit in men than women in cardiovascular diseases

I. Physiological factors

Pregnancy

Causes several physiological changes that influence drug disposition.

- Volume of drug distribution is increased(total body water may increase by up to 8 liters) providing large space for water soluble drugs.
- Maternal plasma albumin concentration is reduced,

  More free drugs will be available

I. Physiological factors

Pregnancy

Metabolic rate is increased, so the free drugs will be available for elimination.

- Cardiac out put is increased, leading to increased renal blood flow and glomerular filtration and increased renal elimination of drugs.
- Lipophilic molecules readily traverse placental barrier. Drugs that are transferred to fetus are slowly eliminated.
- Avoid drugs during pregnancy due to teratogenic effects

pregnant uterus becomes more sensitive to oxytocin

TABLE 9–2 • FDA Pregnancy Risk Categories

Category	Category Description
A	*Remote Risk of Fetal Harm:* Controlled studies in women have been done and have failed to demonstrate a risk of fetal harm during the first trimester, and there is no evidence of risk in later trimesters.
B	*Slightly More Risk Than A:* Animal studies show no fetal risk, but controlled studies have not been done in women *or* animal studies do show a risk of fetal harm, but controlled studies in women have failed to demonstrate a risk during the first trimester, and there is no evidence of risk in later trimesters.
C	*Greater Risk Than B:* Animal studies show a risk of fetal harm, but no controlled studies have been done in women *or* no studies have been done in women or animals.
D	*Proven Risk of Fetal Harm:* Studies in women show proof of fetal damage, but the potential benefits of use during pregnancy may be acceptable despite the risks (eg, treatment of life-threatening disease for which safer drugs are ineffective). A statement on risk will appear in the "WARNINGS" section of drug labeling.
X	*Proven Risk of Fetal Harm:* Studies in women or animals show definite risk of fetal abnormality *or* adverse reaction reports indicate evidence of fetal risk. The risks clearly outweigh any possible benefit. A statement on risk will appear in the "CONTRAINDICATIONS" section of drug labeling.

I. Physiological factors

Lactation

- Avoid drugs during lactation due to harm to baby
- Drugs easily appear in milk

E.g., ***tetracycline, sedatives, hypnotics, opoids***

II.Pathological factors

Diseases can cause individual variations in drug response.

Absorbsion

- Gastric and intestinal stasis during an attack of Migraine interferes absorption of drugs
- Resection of gut may lead to malabsorption of iron,folic acid and fat soluble vitamins and of vit B12 after ileal resection
- Diarrhea increases the motility of the gut and decreases absorption.

Distribution

- Hypoalbuminaemia from any cause such as nephrotic syndrome, burn, malnutrition, sepsis allows higher proportion of albumin free drug in plasma which is readily available for metabolism and elimination
- **there can be risk with initial dose for drugs which are to be highly protein bound (phenytoin, warfarine, tolbutamide)**

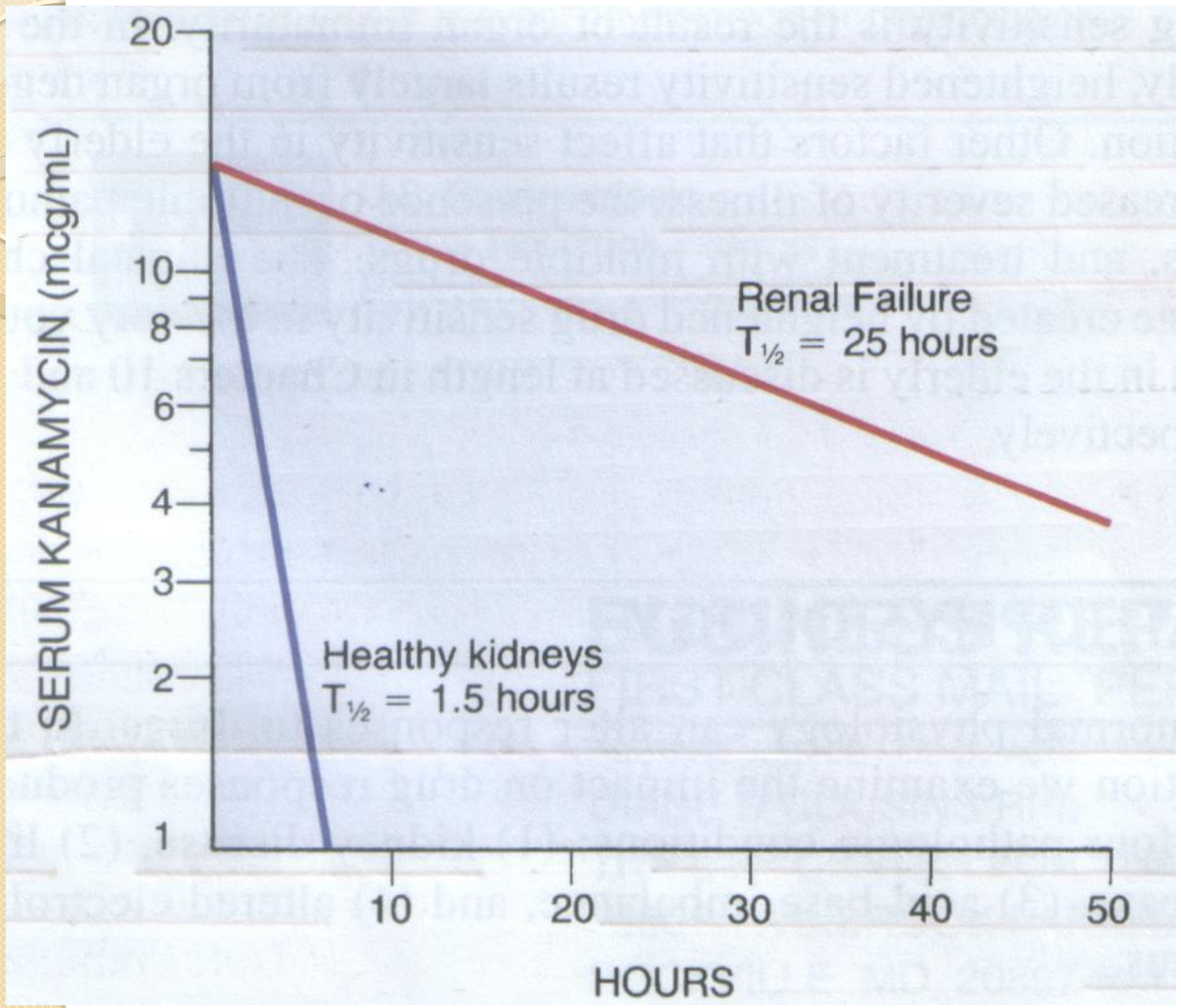
Metabolism

- Acute and chronic diseases of liver affects the blood flow and function of hepatocytes ,leading to decreased drug clearance, and prolong half life (morphine, propranolol, diazepam, rifampicin, theophylinne)

- Drug metabolism is increased in hyperthyrodism and diminished in hypothyroidism

Excreation

- In acute and chronic renal impairment ,concentration of drugs is altered.


SERUM KANAMYCIN (mcg/mL)
20
10
8
6
4
3
2
1
Renal Failure
T½ = 25 hours
Healthy kidneys
T½ = 1.5 hours
10
20
30
40
50
HOURS

- Asthma can be precipitated by beta blocking drugs
- Raised intracrainal pressure ,severe pulmonary insufficiency causes patient to be inttolent to opioids precipitating respiratory failure
- Increased sensitivity of adrenergic receptors in hyperthyroidism.

III. Genetic Factors

Pharmacogenetics

is the study of the relationship b/w genetic factors and drug response.

III. Genetic Factors

GENETIC POLYMORPHISM

The existence in a population of two or more phenotype with respect to the effect of a drug.

III. Genetic Factors

Idiosyncrasy abnormal drug reaction due to genetic disorder .

- Acetylation.
- Oxidation.
- Succinylcholine apnea.
- Glucose 6-phosphate dehydrogenase deficiency.

Acetylation enzymes deficiency

- acetyl transferase (non-microsomal).
- Isoniazid, sulphonamides, etc.
- **Slow** acetylator phenotype → peripheral neuropathy .
- **Rapid** acetylator phenotype → hepatitis.

Oxidation Polymorphism

Debrisoquine.

- Extensive metabolizers (EM) – need larger dose.
- poor metabolizers (PM) – need smaller dose.

Pseudocholinesterase deficiency.

- Succinyl choline (Sk.muscle relaxant) → Succinylcholine apnea due to paralysis of respiratory muscles.

Deficiency of Glucose–6 phosphate dehydrogenase (G-6-PD).

G-6-PD Deficiency in RBCs → hemolytic anemia upon exposure to some oxidizing drugs.

- Antimalarial drug, primaquine.
- Long acting sulphonamides.
- Fava beans (favism).

IV. Environmental factors and diet

Pollutants are capable of inducing P450 enzymes, such as hydrocarbons present in tobacco smoke, grilled meat induce CYP 1A.

Cigarette smokers metabolize some drugs more rapidly than non smokers.

Industrial workers exposed to some pesticides metabolize certain drugs more rapidly than who are non exposed

- Consumption of alcohol induces hepatic microsomal enzyme and increase the metabolism of drugs such as oral contraceptives, theophylline e.t.c.

Grapefruit juice induce CYP3A

Presence of fatty food in stomach delays gastric emptying,

the plasma concentration of rifampicin and ampicillin may be much reduced if taken on full stomach

Protein malnutrition affects pharmacokinetics of several drugs.

- Some drugs have interaction with food and they alter the response of drug
- Calcium in milk interferes with absorption of tetracyclines and iron.
- toxic symptoms appear after eating of cheese, red wine & chicken liver if patient is taking **MAOI** (more release of NA=fatal cerebral hemorrhage)

In conclusion:

To be sure that drug therapy is as safe and effective as possible:

- ✓ *individualization of treatment is essential*
- ✓ *each patient must be monitored for desired responses and adverse responses*
- ✓ *the regimen must be adjusted accordingly*