بسم الله الرحمن الرحيم

# Pharmacodynamics (3)

By
Dr. Mohammad Salem Hareedy

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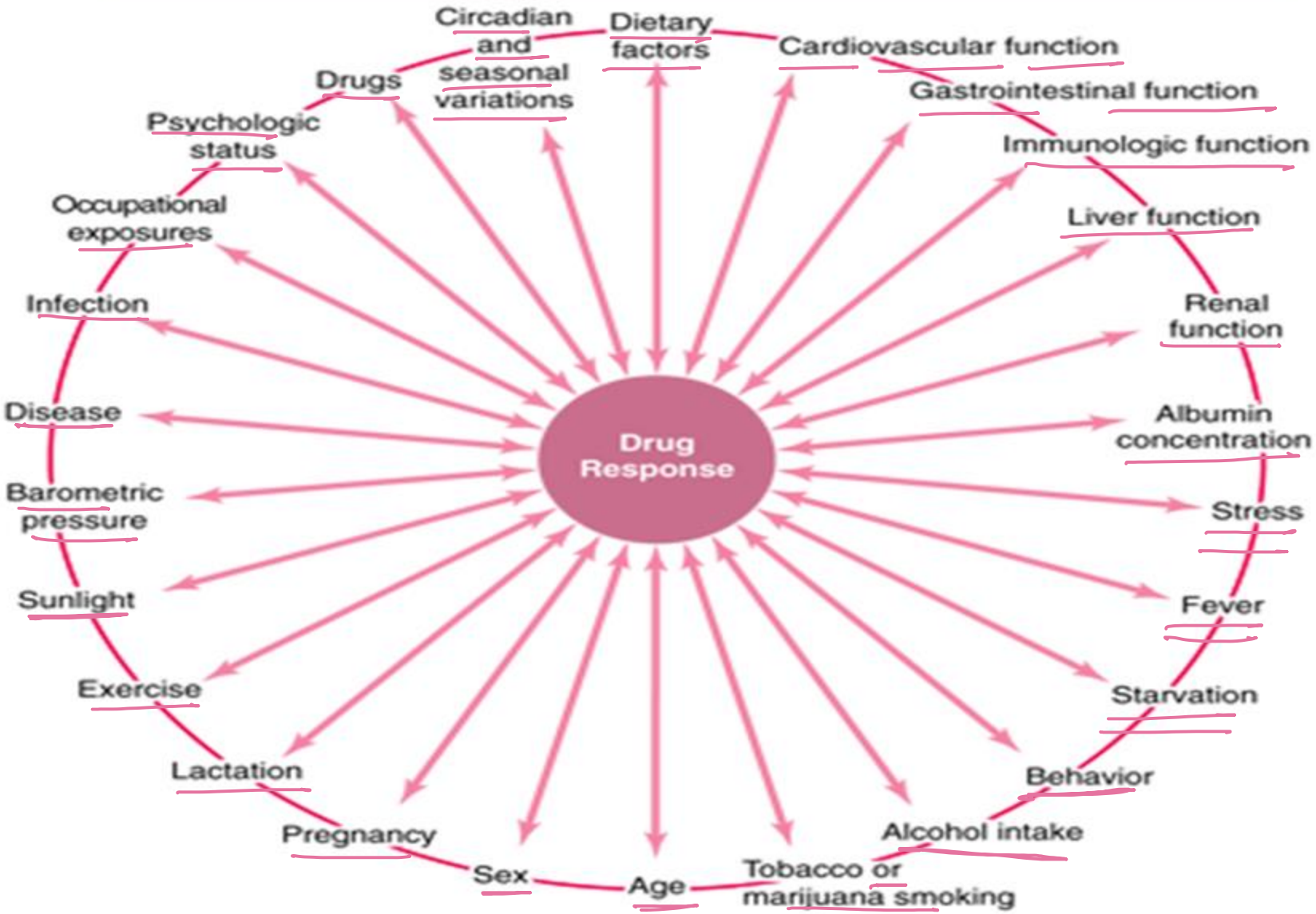
# Factors affecting drug response



1- what're the type of antagonism ?

2- what's the machanism of chemical antagonist ? Give an example ?

3- Give an example about the kinetic ?

4- what's the machanizem of physiological antagonist ?

5- Give an example about these drug ?

# Types of antagonism

## 1-Chemical Antagonists:

One drug may antagonize a second by **binding** to and inactivating the second drug, e.g. protamine (a positively charged protein at physiologic pH) binds heparin (a negatively charged anticoagulant) making it non-functioning. So, protamine is used to treat toxicity caused by heparin. = chemical antagonism of heparin.

## 2 -Kinetic or dispositional antagonists.

Example: One drug (e.g. cholestyramine) may inhibit the absorption of other drug (e.g. digoxin). ✓

↓ cholestrol level

↳ heart faiture

## 3-Physiological Antagonists:

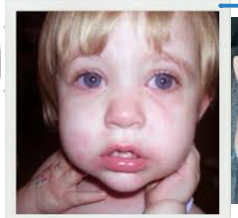
The action of a drug act in the opposite physiological direction of a second drug. → 2 drug → agonist → 2 different receptor.

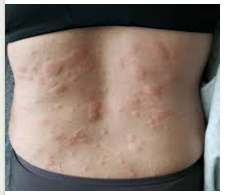
e.g. Glucagon hormone increases blood glucose level while insulin hormone decreases blood glucose level.

So glucagon is used for treating severe hypoglycemia caused by high dose insulin. → opposit action not inhabition of drug action.

Another example is histamine (causes bronchospasm and vasodilatation) and its physiological antagonist adrenaline (causes bronchodilation and vasoconstriction).

Adrenaline is used for treatment of anaphylaxis (i.e. large amounts of histamine are released in the circulation





1-what're the machanizem of pharmacological anagonist ?

2-what're the types of antagonist effect?

# 4-Pharmacological Antagonists (receptor antagonists):

**Drugs** that **bind to same receptors** to which agonists bind but has no intrinsic activity. → one of these drug is agonist and the onther is anagonist

These antagonists may block the ability of agonists to bind to the receptor by competing for the same receptor site or may bind to another site on the receptor that blocks the action of the agonist. In both cases, the biological actions of the agonist are prevented.

Antagonists may be a- ***competitive*** (reversibly displaced by agonists and cause shift of the dose response curve of the agonist to the right) or b- ***non-competitive*** (not reversibly displaced by agonists and cause shift of the dose response curve of the agonist downwards).

1-Explain the machanizem of it?

2- what determine the shifting of curve?

3- Give an example ?

## a) Competitive antagonist (reversible binding)

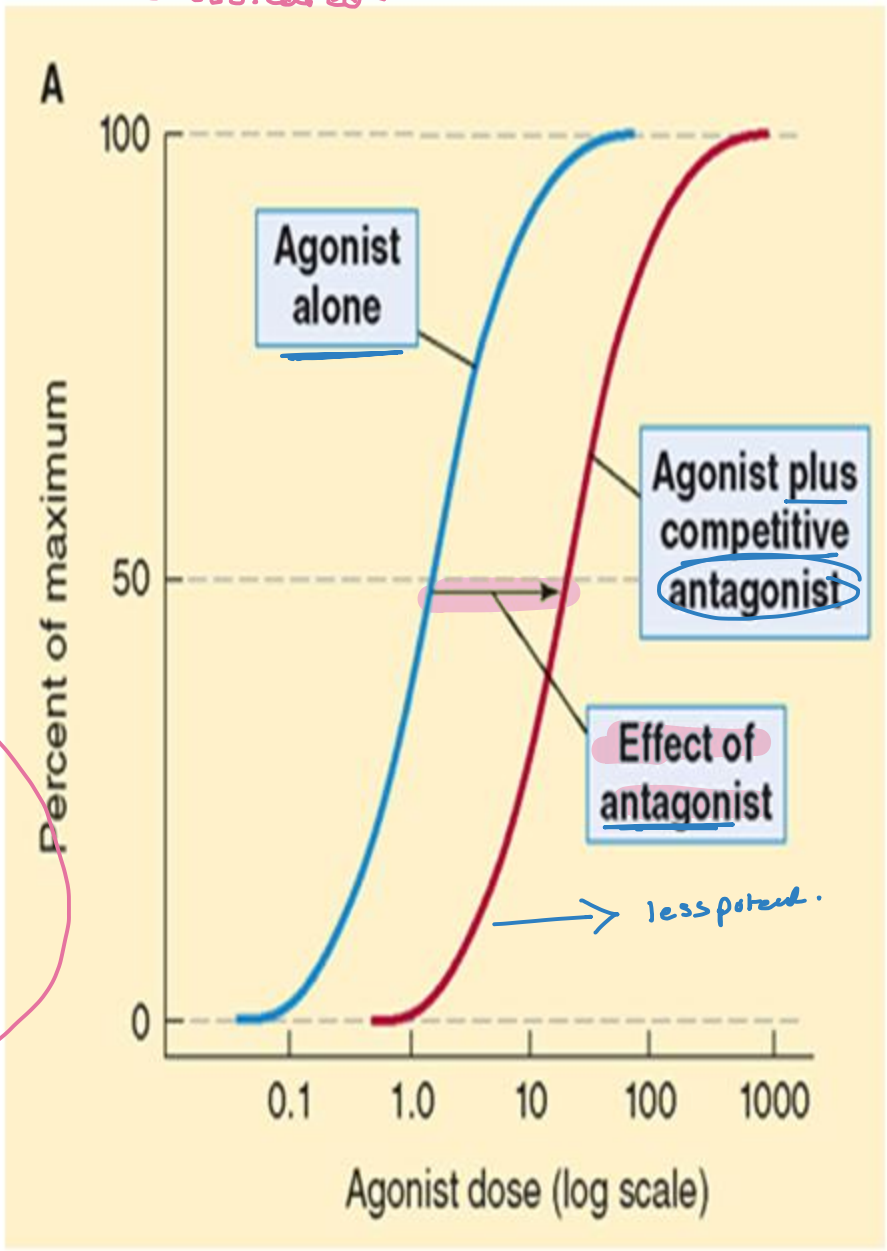
most antagonist

The agonist and its competitive antagonist bind reversibly to the same receptor site.

The game between the two is concentration-dependent

the action of a competitive antagonist can be overcome by using an excess of agonist. This is identified in dose response curve as shift ***to the right.***

***Examples: beta blockers, histamine blockers and atropine.***



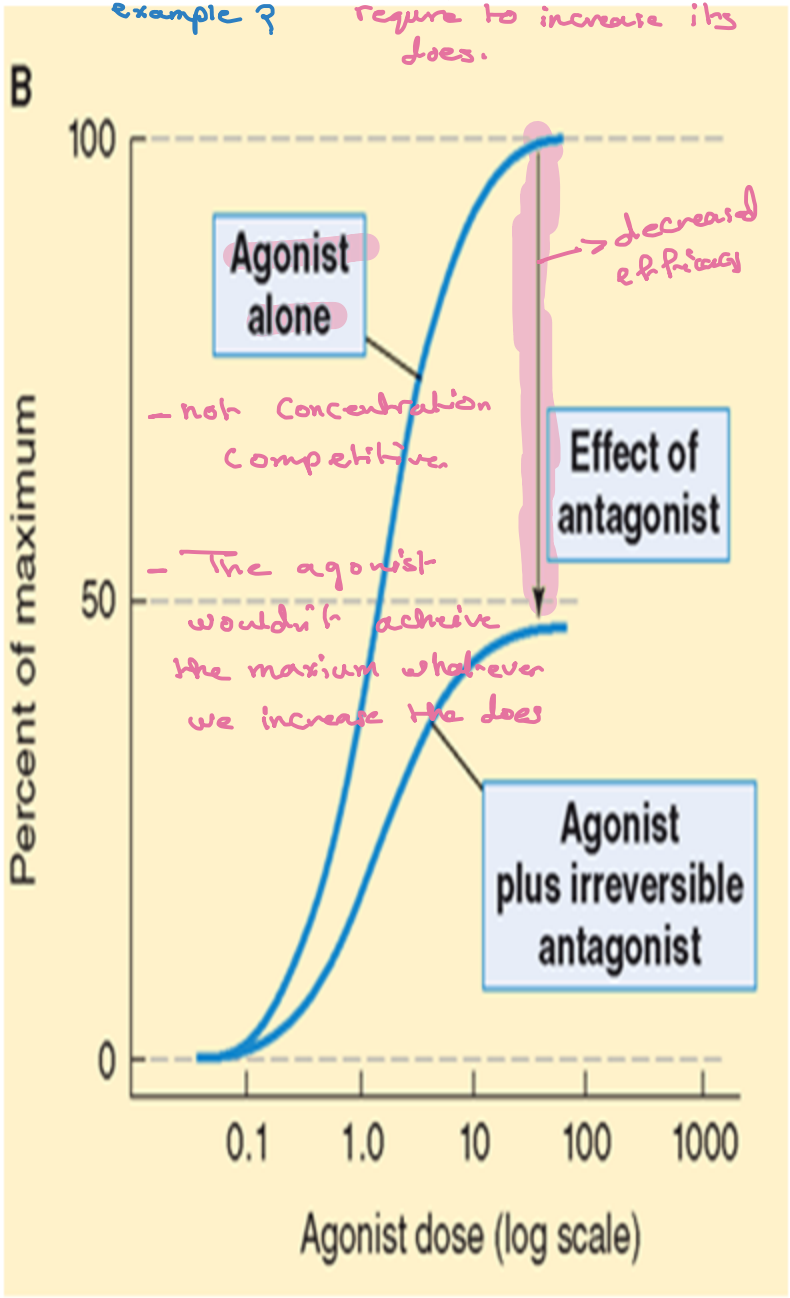

can dissociated.

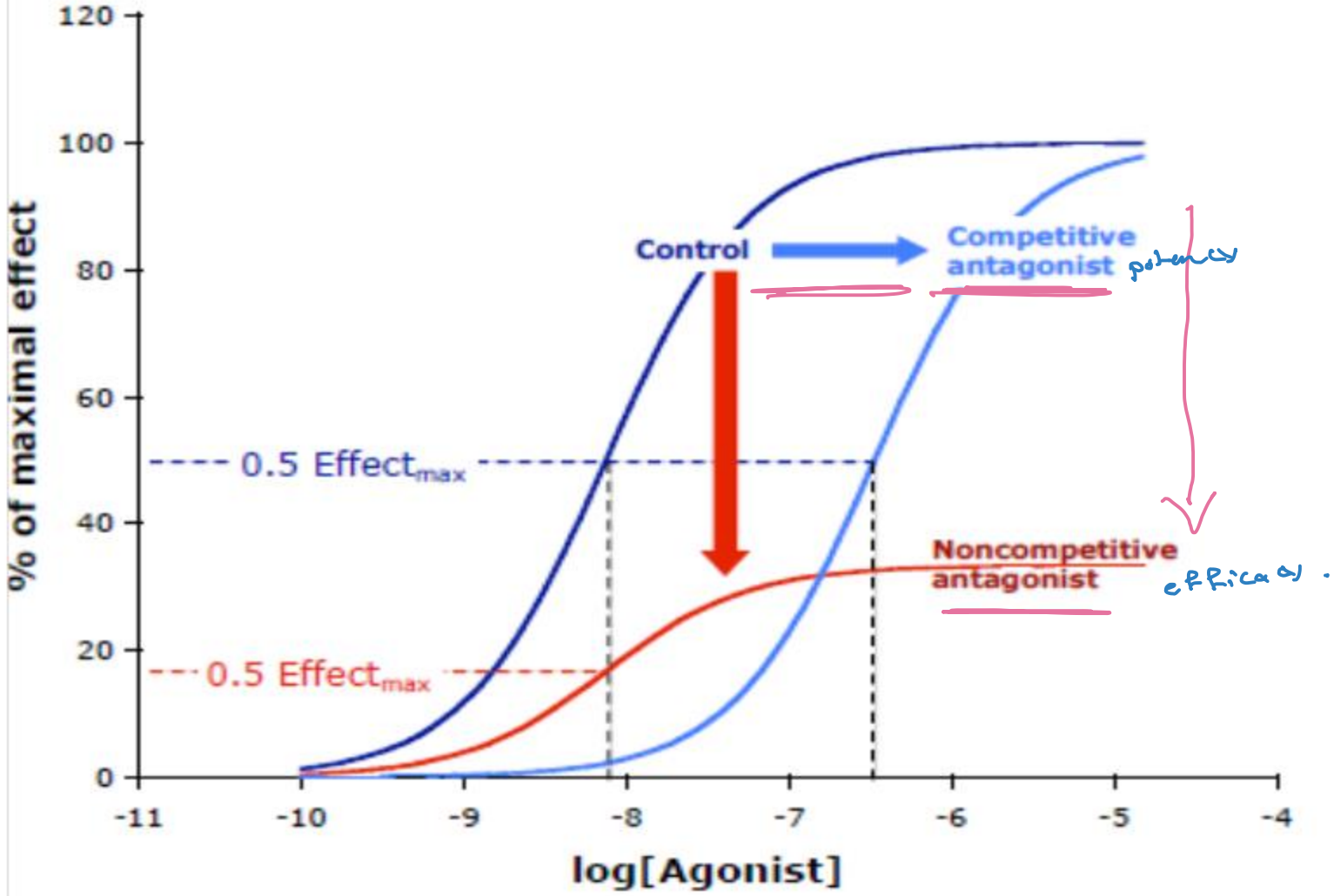
less potent.

The agonist may become more competitive by increasing the does of agonist ——> but this's mean that competive anagonist decrease the potency

1-what is the mechanism of it ? 2-what is the effect of it in the agonist ? 3- Give an example ? of agonist because it requre to increase its does.

**b) Non-competitive antagonist (irreversible binding in most cases or allosteric binding in some cases):** When an antagonist binds **irreversibly** to a receptor (e.g. by **covalent bond**) its effect is not reversed by excess agonist. Increasing the concentration of the agonist in the presence of non-competitive antagonist results in a decrease in the maximal effect obtained usually by the agonist. ✓ ***(downward shift) of the concentration-effect curve. Example is the binding of organophosphorus compounds to cholinergic receptors.***




120
100
80
60
40
20
0
% of maximal effect
Control
Competitive antagonist
potency
0.5 Effect$_{max}$
Noncompetitive antagonist
efficacy
0.5 Effect$_{max}$
-11
-10
-9
-8
-7
-6
-5
-4
log[Agonist]

→ non- competitive antagonist.
→ 90% closed of receptor
→ and give adrenalin (agonist) achieve maxium effect in presence of

# Spare receptors

→ This is due to

spare → receptor not occupied with agonist → when maxium respone is achieved.

Receptors may be considered spare when the **maximal response** is elicited by an **agonist** at a **concentration** that does not produce **full occupancy of the available receptors**. Spare receptors are not different from "non-spare" receptors. They are not hidden. When they are occupied they can be coupled to response.

Spare receptors may be demonstrated by using irreversible antagonists to inhibit binding of agonists to a portion of the receptor pool then demonstrating that a high concentration of agonist may still produce an undiminished maximal response, for example, a maximal inotropic response of heart muscle to catecholamines can be elicited when 90% of the β-adrenoreceptors are occupied by an irreversible antagonist. Thus myocardium is said to contain a large proportion of spare β-adrenoreceptors

1-what is the drug interaction ?
2-what're the type of drug interaction?
3- Explain the beneficial part ? Give an example ?

# Drug interactions

4-what're the type of enhancement factor?
5-what're the harmful effect?

When two or more drugs are given concomitantly, the concentration and/or effects of these drugs can change and this is called drug interaction.


## Beneficial Drug interactions:

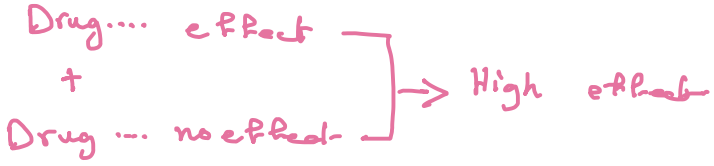
Drug interactions could be beneficial when the therapeutic results of the combination is additive or synergistic (e.g.: **aminoglycosides and beta lactam antibiotic**) or when one drug prevents the adverse effect of another (e.g. **thiazides and spironolactone, magnesium oxide and aluminum hydroxide**).

## Enhancement of drug effect:

**1- Additive effect:** if two drugs with the same effect are given together, the end product is an effect which is equal in magnitude to the sum of their individual effects i.e. 1+1=2

**2- Synergism**: if two drugs with the same effect are given together, the end product is an effect which is greater in magnitude than the sum of their individual effects i.e. 1+1>2

**3- Potentiation:** if a drug which does not have an effect of its own increases the effect of a second active drug i.e. 0+1>1



# Harmful Drug interactions:

In other cases drug interactions could be harmful; if one drug affects the concentration of the other (increased conc. of one drug can cause toxicity and decreased conc. can cause therapeutic failure) or if one drug augments the side effect of the other (e.g. two CNS or cardiac depressant drugs given concurrently).

## Types and mechanisms of drug interactions:

### 1- Pharmacodynamic:

It occurs when a drug affects the pharmacodynamic mechanism of another drug by altering its action at receptor sites. Example is **Morphine** and **naloxone**: which compete with each other at receptor site and naloxone is used to treat morphine poisoning.

→ competitive.

### 2- Pharmacokinetic.

- **Absorption**
- **Distribution**
- **Metabolism**
- **Excretion**

# Factors Affecting the Dose and Action of Drugs

***1. Age:*** In general, children require smaller doses than adults. Either Young's formula (based on age) or **Clark's formula** (based on weight) can be used for calculating the doses for children but the formula based on **body surface area** is more reliable.

***2. Sex:*** This is particularly important in the case of treatment with sex hormones. Female adults generally require smaller doses than males due to the presence of more body fat.

***3. Body weight:*** The usual doses for drugs are mentioned generally for **70 kg adult**.

The dose calculations for abnormally thin or obese patients are required to calculate on the basis of body weight.

## Clark's Rule

$$\frac{\text{Weight (lbs)}}{150} \times \text{Adult dose} = \text{Dose for child}$$

$$\frac{46 \text{ lbs}}{150 \text{ lbs}} \times 12.5 \text{ mg} = \boxed{\begin{array}{l}3.83 \text{ mg} \\ 2 - 3 \text{ x daily}\end{array}}$$

## Young's Rule

$$\frac{\text{Age}}{\text{Age} + 12} \times \text{Adult dose} = \text{Dose for child}$$

$$\frac{5}{5 + 12} \times 12.5 \text{ mg} = \boxed{\begin{array}{l}3.67 \text{ mg} \\ 2 - 3 \text{ x daily}\end{array}}$$

**1 pound (lbs) = 0.45 kilograms (kg)**

***4. Severity of disease:*** It is a common experience that dull headache may be relieved by a single tablet of aspirin whereas severe headache may necessitate administration of 2-3 tablets of the same drug.

***5. Health and nutrition:*** Debilitated and anemic patients are, in general, more sensitive to the toxic effects of drugs and hence they are given smaller doses.

***6. Pathological state:*** For example, phenobarbitone (mainly excreted by the kidneys) should be given in smaller dose in renal failure. morphine should be given in smaller dose for heaptic patients (morphine is mainly inactivated in liver).

***7. Tolerance***

***8. Simultaneous administration of two or more drugs***: May results in addition, synergism or antagonism.

***9. Route of administration:*** In general, the rapidity of absorption of a drug decreases with route of administration in the following order:

Intravenous > Intramuscular > Subcutaneous > Oral. Thus, in general, intravenous (intravenous) dose of a drug is smaller than its intramuscular (intramuscular) or subcutaneous or oral dose.

Example: Doses of ergotamine for various routes are as follows. Oral : 2 to 5 mg; Intramuscular : 1 mg (about to 1/2 of oral dose); Intravenous : 0.25 mg (about to 1/8 of oral dose and 1/4 % of IM dose).

**10. Maternal**, **pediatric** and geriatric considerations.

**11.Genetic factors:** (pharmacogenetic/genomics) which can affect both pharmacokinetics and pharmacodynamics of the drugs.