9

Pharmacology

Doctor 2018 | Medicine | JU

Sheet ○ Slides

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Antagonism between drugs

Pharmacological antagonism | **Physiological antagonism** | **Chemical antagonism**

1- Pharmacological Antagonism

In the last lecture we talked about pharmacological antagonism which can be distinguished from other types of antagonism by understanding **that the antagonist here is competing** with the agonist (endogenous molecule) **to work on the same receptors**. Keep in your mind that the antagonist has an antagonistic action = **blocking the receptor NOT doing the opposite effect of the agonist.**

*Definition: Pharmacologic antagonism: occurs when an antagonist prevents an agonist from interacting with its receptors to produce an effect.

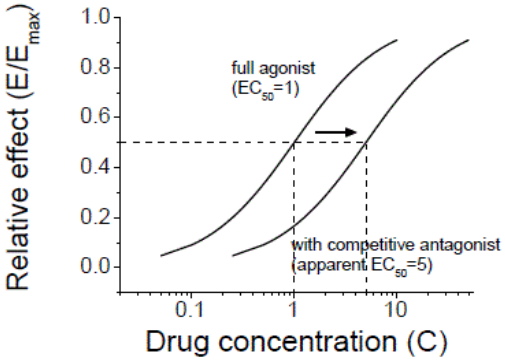
*Types: it can be either competitive or noncompetitive.

a) *Competitive Antagonism*

-The antagonist binds reversibly to the receptors.

-The dose-response curve -> parallel shift to the right

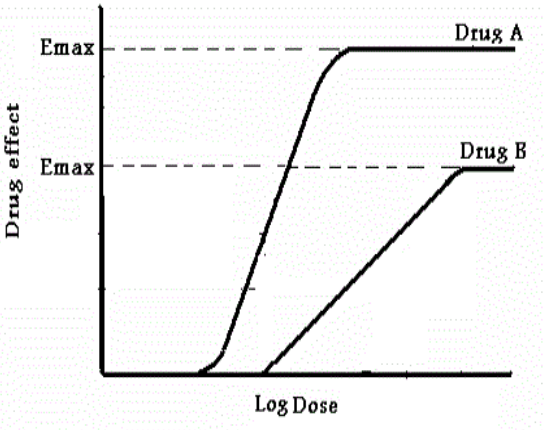
-> increase EC50 of the drug.



b) *Noncompetitive Antagonism*

-The antagonist binds irreversibly to the receptor at the same binding site of the agonist / or the antagonist binds to the allosteric site preventing the binding of the agonist to that receptor.

-The drug-dose curve -> E max decreases -> the shift is non-parallel.



[[That was a summary of what we've just learnt, if you want to read some further explanation, please go to the sheet's post in Facebook 😊 if you have any other questions, don't feel shy to ask me!]]

2-Physiological Antagonism

It can be distinguished by knowing that **the drug acts on a receptor different** than the receptor of the other drug.

*Definition: here the drugs act **independently** on two **different** receptors.

*Examples:

A drug such as **adrenaline** acts on adrenergic receptors. When it binds, it causes dilation of bronchi / constriction of blood vessels.

While **histamine** will act on **different receptors** independently, causing the opposite effects of adrenaline. Therefore, leading to constriction of bronchi and dilation of blood vessels.

Here we call Histamine= agonist, while adrenaline= physiological antagonist.

That's why if someone has an allergy for a drug, we give him adrenaline to save his life ^^

When an anaphylactic reaction* occurs, it causes swelling of the tongue and the throat+ hypotension because of dilation of blood vessels. All these signs and symptoms are because of histamine.

To counteract this effect, we give the patient adrenaline resulting in dilation of bronchi+ constriction of blood vessels.

الأدرينالين قوي وسريع و يرتبط على receptors مستقبلات موجودة في كل أنحاء الجسم في نفس الوقت

*Anaphylactic reaction is an adverse immunological reaction to a compound (food or drugs).

تفاعل حساسية مفرطة

Same concept is applied on drugs that act on the sympathetic nervous system (causing the heart rate to increase and vasoconstriction) and those that act on the parasympathetic nervous system (decreasing the heart rate and causing vasodilation).

3- Chemical Antagonism (Antagonism by neutralization):

It can be distinguished that it includes a reaction between acidic and basic drugs.

*Definition: it occurs when two drugs combine with one another to form an inactive compound.

*Examples:

1) Antacids (anti acids) react chemically with HCl in the stomach neutralizing the acidity of it.

2) Some drugs that are used to treat toxicity, contain sulfhydryl groups (-SH), which will bind to mercury or arsenic. As a consequence, the toxicity of these harmful metals is eliminated.

Enhancement of drug effects

Happens when there is a combination of two drugs each of them has positive/ enhancement effects. There are three kinds of these effects:

1) Additive effect:

*Definition: If two drugs are given together, the net effect of the two drugs will be equal to the sum of the effect of each of them individually. *1+1=2*

*Example: Paracetamol reduces pain by 40% and ibuprofen reduces pain by 50%. If there is a pain reducing by 90%, we can say that the effect here is an additive effect *50% + 40% = 90%*

2) Synergic drug effect:

*Definition: If two drugs are given together, the net effect of the two drugs is higher than the sum of the effect of each of them individually. *1+1>2*

*Example: there are two antibiotics, one kills bacteria by 30%, the other kills bacteria by 40%, but COMBAINING them together kills bacteria by 90%. *30% + 40% > 70%*. We can say that these two antibiotics synergy the effects of each other.

معنى synergy (يؤازر/ يناصر)

3) Potentiation drug effect:

*Definition: if two drugs are given together, one of them alone has an effect of 1, the other doesn't have an effect on its own (effect=0), but **COMBAINING** them together will increase the effect of the first drug to more than one. *1+0 >1*

*Example: Amoclan is a powerful antibiotic, which is a combination of two drugs, one of them is called Amoxicillin, and the other is called Clavulanic acid.

Amoxicillin – kills bacteria (penicillin)

Clavulanic acid – doesn't kill bacteria on its own.

But when we give the two together, clavulanic acid enhances (increases) the strength of amoxicillin to kill bacteria.

Why does this happen? Amoxicillin (penicillin) kills bacteria by inhibiting the synthesis of cell wall.

After a long period of using antibiotics to kill bacteria. Some **bacteria** have developed **resistance** to **antibiotics** that were once commonly used to treat them by certain mechanisms. One of these mechanisms was by the production of an enzyme that degrades amoxicillin (penicillin), called penicillinase.

In this case, amoxicillin (penicillin) will only kill the bacteria that don't produce penicillinase.

So, we add clavulanic acid, which doesn't kill the bacteria, but rather, inhibits the activity of penicillinase.

للتبسيط، البنسلين لوحده قادر على قتل البكتيريا عن طريق إيقاف بناء الجدار الخلوي ولكن بعد فترة من استخدامنا له تبدأ البكتيريا في البحث عن طرق من أجل حماية نفسها منه كي تبقى حية ، فأصبحت بعض البكتيريا تقاوم البنسلين عن طريق إنتاج إنزيم يكسره -_- لكن ان استخدمت البنسلين لوحده سوف يقتل جزء من البكتيريا (الخالية من ذلك الانزيم) ويبقى الجزء الآخر منها على قيد الحياة (التي يوجد فيها الانزيم الذي يكسر البنسلين) و عند إضافة clavulanic acid سيثبط عمل الانزيم الذي يكسر البنسلين فيصبح البنسلين قادرا على قتل البكتيريا القاومته زمان..

To summarize: Properties of an Ideal Drug:

Effective.

Safety (=therapeutic index).

Selective.

Reversible Action.

Predictable (=know what is the effects and side effects of the drugs)

Freedom from drug interactions

Low cost & chemically stable

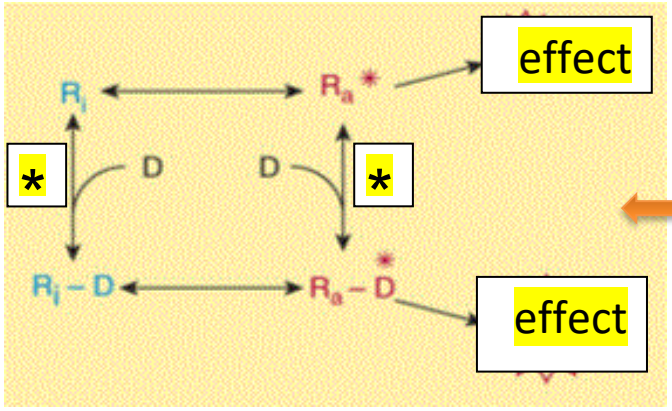
We already know **the lock and key theory** that explains how the drug causes the clinical effect by binding to the receptors. The theory assumes that the lock is the receptor and the key is the drug. This is the traditional theory of drug-receptor interaction.

Now, we have a new theory called:

The two-state model of drug-receptor interaction

) The receptor without the presence of any ligand or agonist keeps switching its conformation between the inactive form (Ri) and the active form (Ra).

*) The agonist/ drug will shift the conformation more toward the active one.



By these two points, we can understand what the terms "full agonist" and "partial agonist" mean.

"Full agonist ": A drug that binds to the receptor and moves it fully toward the active conformation.

"Partial agonist": A drug that binds to the receptor and moves it partially toward the active conformation

*في الصورة العلوية هناك حالة من الاتزان equilibrium بين المستقبل الفعال و غير الفعال (active _receptor \ inactive) حتى وان لم يكن مرتبطا بشيء ولكن اذا ارتبط بهذا المستقبل دواء سوف يجعل التفاعل يتجه أكثر نحو (active) ومن الممكن ان يتجه كلياً نحو حالة (active) فيعتبر full agonist او يتجه قليلا نحو التفاعل العكسي (inactive) فيعتبر partial agonist

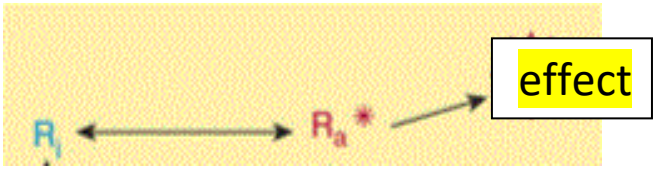
فلنفترض أنه full agonist و partial agonist ارتبطوا بنفس العدد من (receptors) سنجد ان full agonist اعطى (effect) بنسبة 100% تقريباً بينما الpartial اعطى بنسبة 80% وهذا بسبب عدد (receptors) التي اصبحت active

NOTE: The ability of the receptor to start the signaling cascade and produce clinical effects without the need for agonists is called **Constitutive Activity.**

توضيحاً لنقطة 1 بالصفحة السابقة سبق وان قلنا انه حتى وان لم يكن هناك شيء مرتبط بالمستقبل سوف يكون هنالك حالة اتزان بين حالتيه الفعالة والغير فعالة (equilibrium بين active وinactive) وقدرته هذه (أن يكون فعالا active رغم غياب المادة التي ترتبط به) نسميها constitutive activity و هذا واضح في أول سطر في الصورة

ACTIVE ---------> EFFECT

The recognition of constitutive activity may depend on the receptor density, the concentration of coupling molecules (if a coupled system), and the number of effectors in the system.



This brings us to another topic:

Inverse agonist:

It is a drug that binds to the receptor and moves it to the inactive conformation (Ri).

-What is the difference between competitive antagonist and inverse agonist?

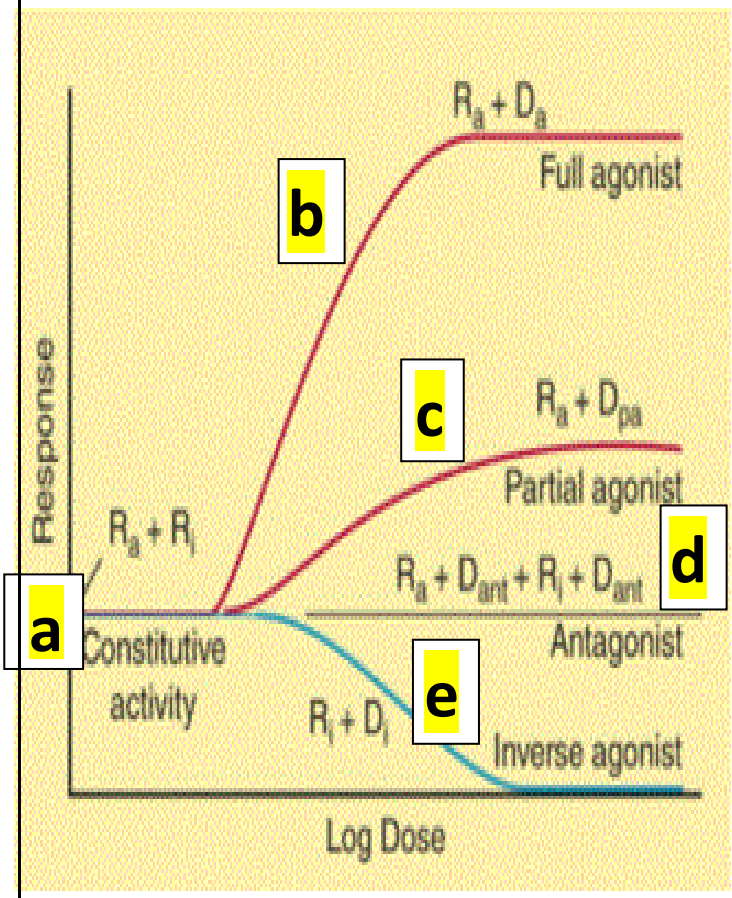
As we already said, **a competitive antagonist** doesn't cause any effect, it just binds and blocks the receptors, WITHOUT shifting the equilibrium towards the active or inactive form.

But **an inverse agonist,** shifts the equilibrium toward the inactive form- it is considered a type of antagonists because it reduces the activity of the receptors below the constitutive activity.

-When do we need the inverse agonist?

We can design drugs that change the conformation of the receptors more toward the inactive ones (inverse agonists), especially for those receptors that have ***high constitutive activity***.

-Example: There are some receptors in the brain that have high constitutive activity, like those which inhibit the transmission of brain signals to neurons -> cause sleepiness.



The inverse agonists will bind to these receptors-> shift them to the inactive form -> activation of transmission.

To summarize, let's study the curves below:

a) Notice that the **constitutive activity** is NOT zero, meaning that in the absence of any drug or ligand, we can still observe some response).

b) The drug that shifts the receptors *fully* toward active ones is called **full agonist**.

c) The drug that shifts the receptors *partially* toward active ones is called **partial agonist**.

d) The drug that does has no impact on the constitutive activity is called **antagonist**/ neutral (=competitive) antagonist.

e) The drug that causes a decrease in the constitutive activity is called **Inverse agonist** (causes shift of equilibrium toward inactive conformation)

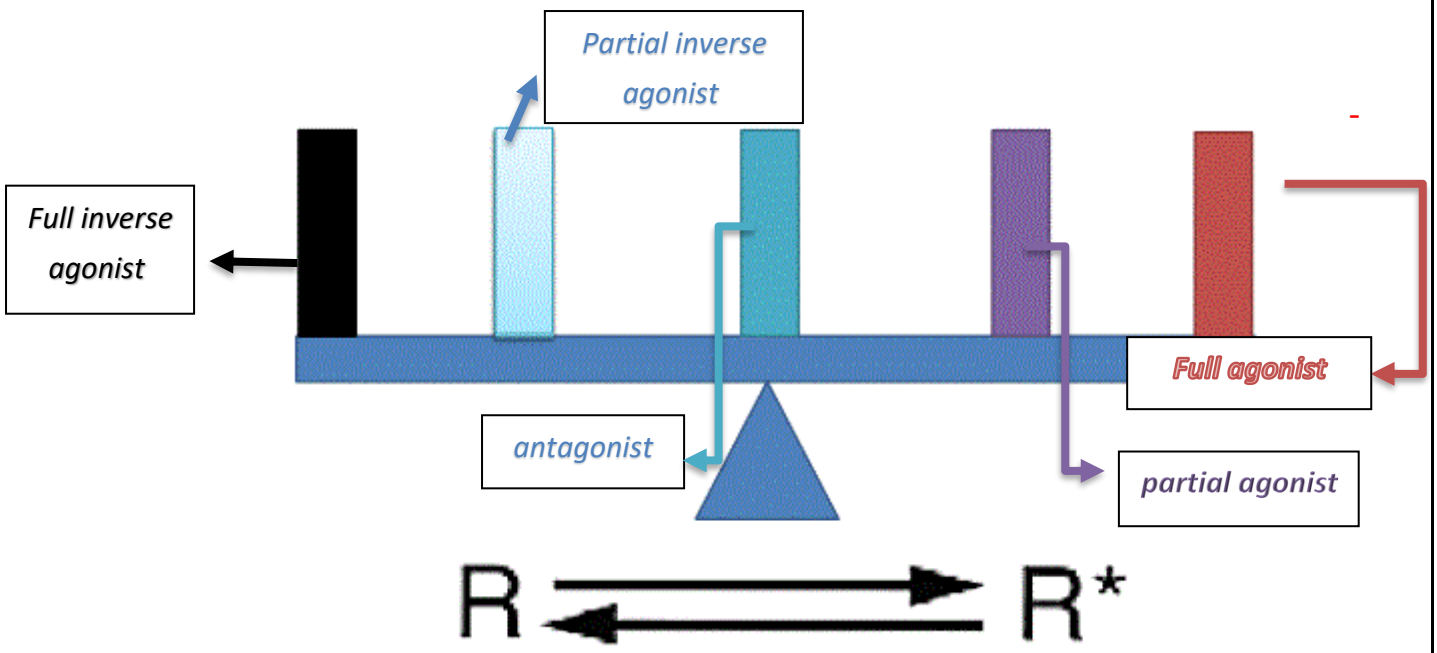
**we have studied until now, that the receptors always exist in two forms: active/ inactive

but what determines which form they can stay in?

Thermodynamic considerations indicate that even in the absence of any agonist, some of the receptor pool must exist in the Ra form some of the time and may produce the same physiologic effect as agonist induced activity.

-if we add Agonists that have a much higher affinity for the Ra configuration and stabilize it -> a large percentage of the total pool resides in the Ra–D fraction -> a large effect is produced.

ذلك يعني أن receptor سوف يكون دائما بين حالتين (active\inactive)حتى بعدم وجود agonist، إذا وجد agonistسوف يقلل الطاقة الخاصة بال receptor مما يعني انه مستقر اكثر وهكذا يتواجد بحالته الفعالة اكثر, وإما ان يحولهم كلهم الى full active او يحول جزء منهم partial active وهذا يعتمد على مقدار تقليل الطاقة وبهذا يجعل (receptor) اكثر استقرار



Drugs reduce the energy that is needed for the receptor to stay in the conformation.

نفس الأفكار المذكورة سابقا لكن بتمثيل مختلف لكل نوع اين سيسحب التفاعل باي اتجاه R=inactive أوR*=active

Sometimes we use the partial agonist as an antagonist

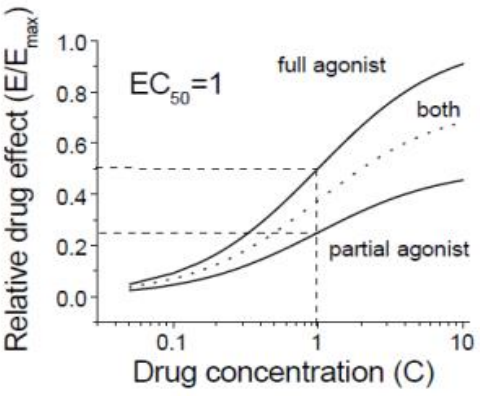
when both a full agonist and partial agonist are present, the partial agonist actually acts as a competitive antagonist, competing with the full agonist for receptor occupancy and producing a net decrease in the receptor activation observed with the full agonist alone-> In this case, we need higher concentration of the full agonist to reach 50% of E max -> increase EC50 of the full agonist.

Example:

-**Nicotine** is a full agonist to nicotine receptors -> giving the max effect (=1)

-**Chantix** is a partial agonist to nicotine receptors -> increases EC50 of nicotine.

So, the patient, that is taking Chantix beside the same dose of nicotine he used to take, is not receiving the same therapeutic effect – helping him to decrease the dose of nicotine gradually.



Variation in drug responses

Sources of Variability in Therapeutic Responses

Similar drugs usually produce similar qualities of responses in patients, but might produce different intensities and duration of effects.

- Dose, Dosage schedule, and Route of administration.
- Diurnal variation "Chronopharmacology".
- Age and sex of the patient.
- Drug reactions.
- Drug interactions: other drugs, diet, and environment.
- Placebo effect.
- Intercurrent illnesses.
- Tolerance.
- Genetic or racial factors, "Pharmacogenetics".

Causes of Variability in Drug Response

A)Those related to the biological system:

1- **Genetics – pharmacogenetics** (example: cytochrome p450)

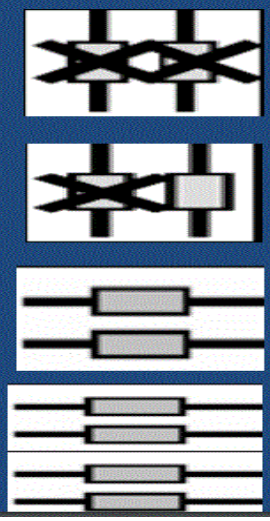
Phenotypes of CYP450

1. Poor metabolizer (PM)
- has low metabolic capacity
- has two mutant alleles

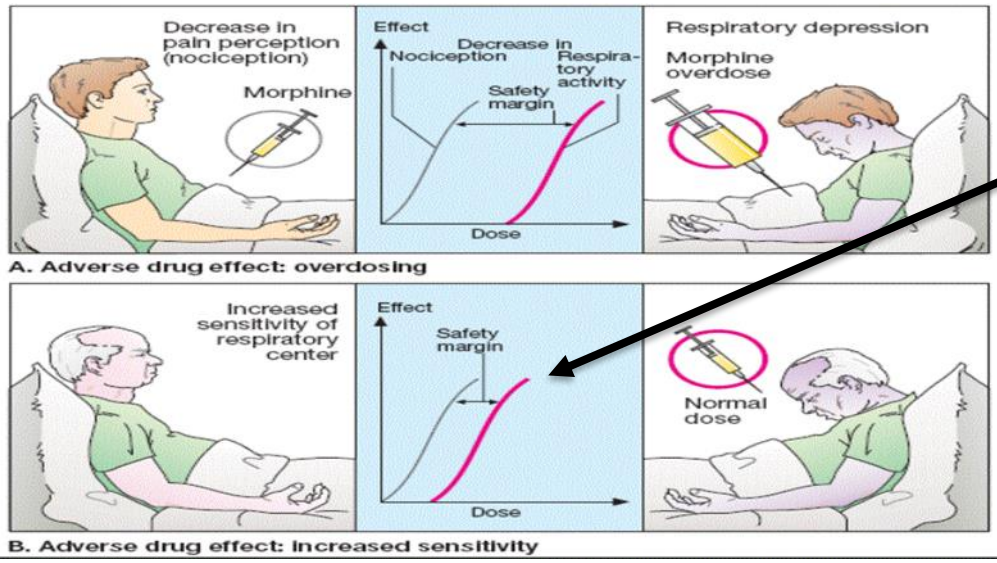
2. Intermediate metabolizer (IM)
- has metabolic capacity between PM and EM
-has one reduced activity allele and one null

3. Extensive metabolizer (EM)
- has regular metabolic capacity
- has at least one and no more than two normal functioning alleles

4. Ultrarapid metabolizer (UM)
- has higher metabolic capacity than EM
- has multiple copies of functional alleles



2- **Age and Sex** (we don't treat elderly patients as we do for young individuals. We must take into consideration that certain changes might happen in the body of these elderly patients affecting pharmacokinetics and pharmacodynamics of the drugs).



Margin of safety is less

20% of hospitalizations for those >65 are due to medications they're taking

Changes in pharmacokinetics of elderlies:

-**Decrease in total body water (due to decrease in muscle mass) and increase in total body fat affects volume of distribution**

• Water soluble drugs: lithium, aminoglycosides, alcohol, digoxin – Serum levels may go up due to decreased volume of distribution

• Fat soluble: diazepam, thiopental, trazadone – Half-life increased with increase in body fat

-**Oxidative metabolism through cytochrome P450 system does decrease with aging, resulting in a decreased clearance of drugs**

-**GFR generally declines with aging, but is extremely variable**

• 30% have little change

• 30% have moderate decrease

• 30% have severe decrease

• Serum creatinine (Scr) is an unreliable marker

• If accuracy needed, do Creatinine Clearance (CrCl)

Age	Scr	CrCl
30	1.1	65
50	1.1	53
70	1.1	41
90	1.1	30

Changes in pharmacodynamics of elderlies:

Increase sensitivity to sedation and psychomotor impairment with benzodiazepines

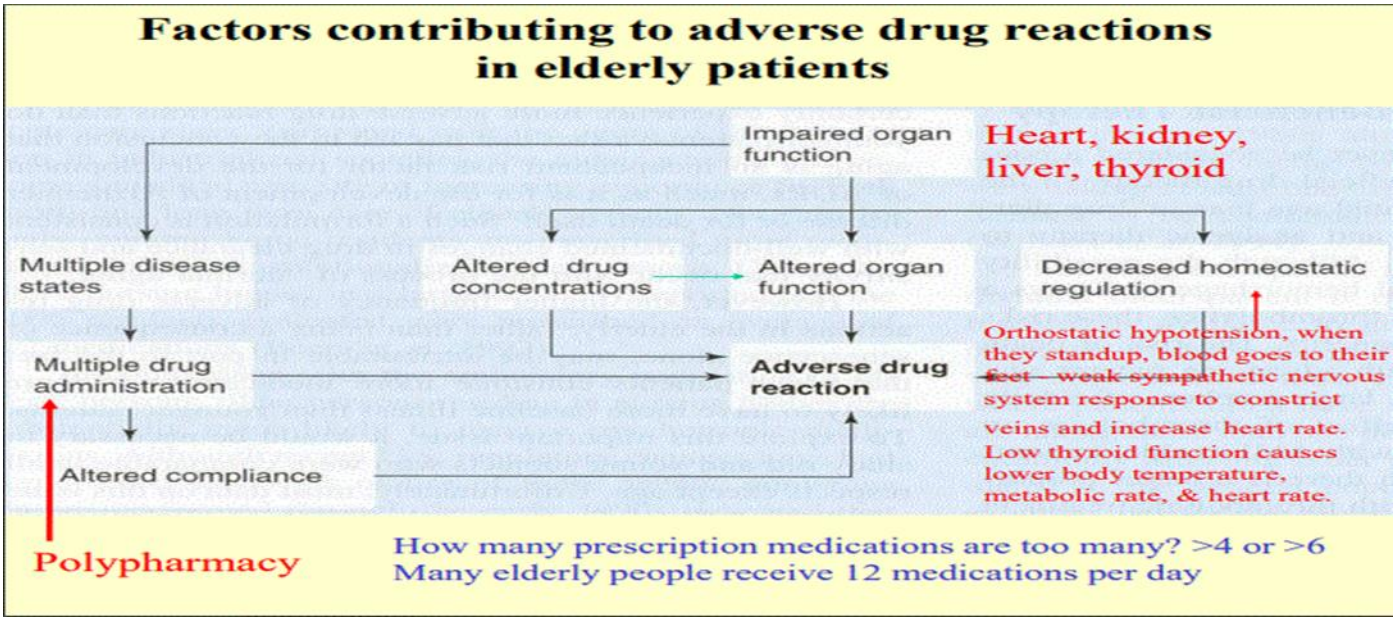
Increase level and duration of pain relief with narcotic agents

increase drowsiness and lateral sway with alcohol

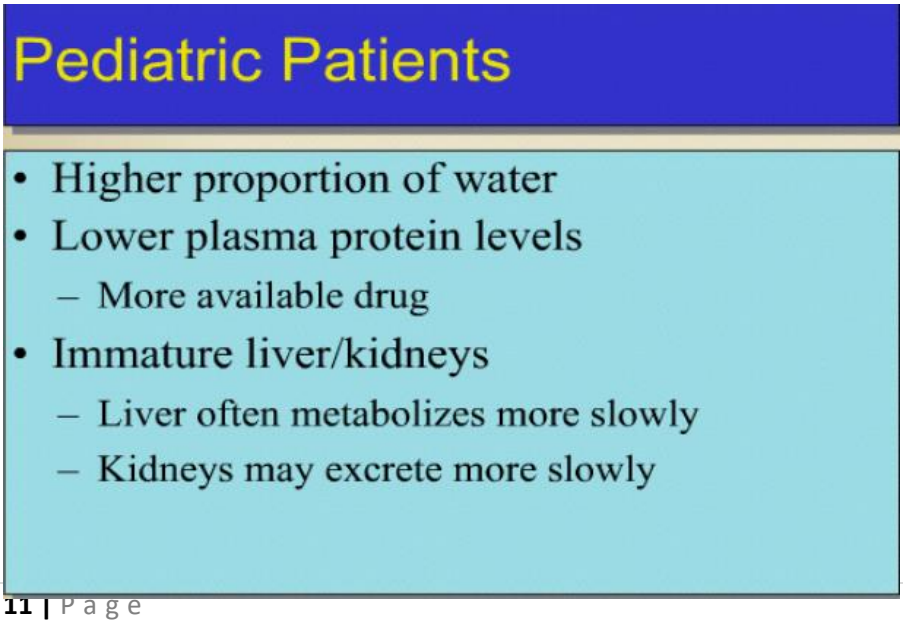
decrease HR response to beta-blockers

increase sensitivity to anti-cholinergic agents

increase cardiac sensitivity to digoxin



3- **Body weight and size**:



->Traditionally, for less frequently used drugs, extrapolation is done from **adult** dose on a weight or surface area basis

-> but **children are NOT small adults**; they don't have mature kidneys and liver

-> problems:

• **Absorption may be more or less than adults**

• **Clearance of some drugs in children is affected by maturation, as well as size, examples:**

1- Cytochrome P450 enzyme system matures over time

2- Glomerular filtration changes over time

3- CYP Enzymes: CYP isoforms vary with age. For example, clearance of midazolam by CYP 3A4 and 3A5 goes from 1.2 ml/min/kg to 9 ml/min/kg over first few months of life

4- Carbamazepine (3A4) clearance faster in children than adults – requires higher doses

• **Drug targets may vary with age**

4-**Condition of health** (the liver of hepatitis patient will not function as the liver of a normal person)

5- **Placebo effect** (the effect of psychology of the patient...)

B) Those related to the conditions of administration:

1-Dose, formulation and route of administration.

2-Resulting from repeated administration of drug (drug resistance; drug **tolerance**- tachyphylaxis; drug allergy)

3- **Drug interactions (**chemical or physical, GI absorption, protein binding/distribution, metabolism (stimulation/inhibition), excretion (pH/transport processes), receptor (potentiation/antagonism), changes in pH or electrolytes.**)**

continuous use of drug -> decreases response to the drug -> because of the decrease in receptors number (to maintain homeostasis/ down regulation) which have different consequences on the body.

Drug-drug interactions

When two drugs taken together, there is a possibility that the drugs will **interact** with each other to cause **unanticipated** effect. Usually increase or decrease in the desired therapeutic effect.

Drug-drug interaction can occur in the following sites

*) At the site of absorption, tetracycline is not absorbed from the GI tract if calcium product is present in the stomach.

*) During biotransformation (CYP 450).

*) At the site of action (where the drug will interact with the receptor), drug antagonism.

*) During excretion, digoxin and quinidine are both excreted from the same sites in the kidney. The quinidine will be excreted first because it is more competitive for these sites, resulting in increased serum levels of digoxin.

*) During distribution, aspirin competes with methotrexate for protein binding sites, and because aspirin is more competitive for the sites, that results in an increased release of methotrexate and so increased toxicity to tissues.

Adverse effects

Adverse effects are **undesired effect** that may be unpleasant or even dangerous.

they can occur for many reasons:

1. The drug may have other effects on the body besides the therapeutic effect.

2. The patient is sensitive to the drug.

3. The patient is taking too much or too little of the drug.

Remember!!!

- With every drug use, unwanted effects must be taken into account.
- Before prescribing a drug, the physician should therefore assess the **risk: benefit ratio**.
- In this, knowledge of principal and adverse effects is a prerequisite.

Adverse Drug Reaction

• Adverse drug reactions are classified as **predictable or unpredictable**.

• A **predictable drug reaction** is related to the pharmacological actions of the drug.

• An **unpredictable reaction** is related to immunological response (hypersensitivity reactions) or non-immunological response

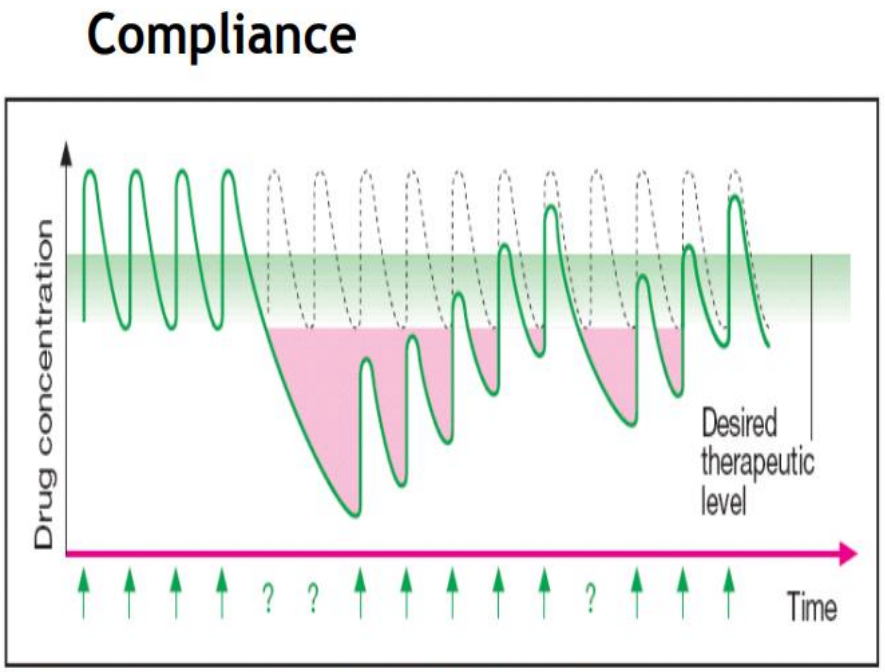
Drug Allergy

• It is defined as an **adverse reaction** to a drug by a specific immune response either **directly** to the drug or one or more of its metabolites alone, or to a **drug bound** to a body protein such as albumin, (Hapten).

• Such binding **alters** the structure of the drug/ protein complex, rendering it **antigenic**.

EXTRA INFORMATIONS:

Irregular dosing, such as occurs with the increased nocturnal dosing interval with fixed-dose/fixed-time-interval regimens or due to missed doses (poor patient compliance), results in the plasma drug concentration falling below the desired therapeutic level (*pink areas*). It then takes several doses to reach the desired therapeutic level once again. Note that the arrows signify when each dose of drug is taken and the question mark (?) represents a missed dose.



Time course of drug concentration with irregular intake

وكما قالت ريمي

"اياك ان تفرط في ذلك الحلم الذي عقدت العزم على تحقيقه سيتحقق الحلم ان امتلكت العزيمة والإصرار"