النادي الطبي

MC

راضي

Done By :
Baraa Safi

لا تنسونا من دعائكم بالتوفيق

5) Microsomal enzyme induction can be a cause of:

A. Tolerance

1-Centrally acting O_2- Agonists

- Clonidine -

هاد اهم

Methyldopa

-Guanafacin

-guanabenz

2-Ganglion Blockers

- Trimethaphan (I.V. infusion).

mechanism احفظوهم ك اسماء بس مش رح ناخد

2

3

3-Adrenergic Neuron Blockers

Guanethidine.

Reserpine.

The sympathetic and parasympathetic nervous systems have opposite responses on body tissues and organs.

Classification

receptor blockers

- Selective α1-blockers:
- Doxazocin
- Prazocin
- Terazocin
- Tamsulosine
- Trimazosine

هدول بس

ماشي

+ المحاضرة إلي قبل

- Non Selective α-blockers - بتقفل الاثنين
- Phenoxybenzamine
- Phentolamine
- Tolazoline

- Selective α2-blockers
- Yohambine

ماخ تيابلا
غيرهون صالاسم

bb

Non-selective beta blockers

- Propranolol
- ~~Propranolol~~ pindolol
- Nadolol
- Timolol

4) Aprodrug is:

A. The prototype member of a class of drugs

B. The oldest member of a class of drugs

C. An inactive drug that is transformed in the body to an active metabolite

D. A drug that is stored in body tissues and is then gradually released in the circulation

[5] Drug intolerance (hyperreactivity or hypersusceptibility): = withdrawl effect

Effect Of Leukotrienes

ايش بتعمل هاي ال leukotriens؟

inflammatory mediator

1-Leukotrienes are biologically active **components of Slow Reacting Substances (SRS-A).** causes fluid leakage from blood vessels to an inflamed area

يعني رح تزيد الاستجابة الالتهابية

2-Leukotrienes are **100-1000 times more potent** than **Histamine** during **allergic reactions**

يعني كمائيتها خلال الالتهاب أكبر من الهستامين

SRS-A are released during **Allergic reactions/Anaphylaxis.**

3-LTB_4 is a potent **chemotactic agent.**
(chemical substance which mediates movement of cells).

4-Leukotrienes by action are:

Bronchoconstrictors

Vasoconstrictors -

Levels Of Leukotrienes Increased In:

Allergies

التهاب الأنف

Allergic rhinitis

Asthma

Overproduction: **Anaphylactic shocks.**

Net excretion = GF + TS - TR

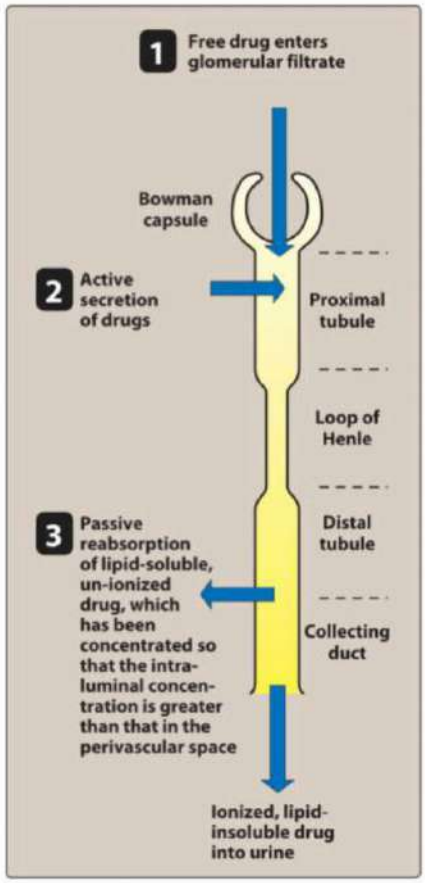
⇓

If the net excretion is 120 = excretion through GF

If the net excretion is more than 120 = Secretion mechanism

If the net excretion is less than 120 = Reabsorption dependance

مهم جدًا، ويجي عليه سؤال



DRUG INTERACTIONS MAY BE ANTAGONISTIC

مطلوب حفظ اول مثال واخر مثال

PRIMARY DRUG	INTERACTS WITH	RESULTING IN
SALBUTAMOL	-PROPRANOLOL	ANTIAGONISM OF BRONCHODILATION
ANTIHYPER-TENSIVES	-NSAIDS	ANTAGONISM OF HYPOTENSIVE EFFECT (Na^+ - RETENTION)
	- SELECTIVE COX 2 INHIBITORS	NO SIGNIFICANT EFFECTS ON Na
SULPHONAMIDES	-L. ANAESTHETICS -(PABA)	ANTAGONISM OF ANTIMICROBIAL EFFECTS
WARFARIN	OESTROGENS	WARFARIN EFFECT ANTAGONIZED BY INCREASED CLOTTING FACTOR SYNTHESIS
OPIOIDS	NALOXONE	ANTAGONISM

Clinical significance of Enzyme Induction:

- Drugs stimulating the microsomal enzyme systems → ↑ activity →
  - ↑ their own metabolism → **tolerance** e.g. **phenobaritone.**
  - ↑ metabolism of other drugs metabolized by these enzymes and are given at same time → drug interactions e.g.:
    - **Rifampicin** →↑ **oral contraceptive** metabolism → pregnancy
    - **Phenytoin** →↑ **cyclosporine** metabolism → transplant rejection
    - **Rifampicin** →↑ **warfarin** metabolism → therapeutic failure.
  - ↑ metabolism of endogenous substrates e.g. **phenobarbitone** → ↑ elimination of **bilirubin** → used in treatment of neonatal jaundice)
  - ↑ metabolism of vitamins e.g. phenytoin → ↑ of vit.D, vit.K, folic acid → osteomalacia, bleeding and megaloplastic anemia

Significance of clearance الأهمية

1. Calculation of the maintenance dose **(MD)**
2. Adjustment of the **dosing regimen** for drugs eliminated by glomerular filtration e.g. dosing of gentamicin

	Atropine	hyoscine
Duration of action	Long duration 7-10 days	Short duration 4-7 hours
Action :1-dominant PS action	CVS , GIT, Urinary حاجات جامدة	Eye and secretions ✓ حاجات رخوة
2- CNS	Both stimulant and depressant but mainly stimulant الشخص لما يركب سيارة أو طيارة ... بيفرغ بالدوار، الحل إنه أمكن مستقبلات M في CNS عشان توقف هاد الإحساس زي (atropine) بس بنستخدمه أكثر لأنه مشاكله أقل	Both stimulant and depressant but mainly depressant -sedation, hypnosis and - -amnesia to recent events -Antimotion sickness -Antiparkinsonial هاد المهم بس
		~~Stimulant effect ++PC Excitation and hallucination with over dose~~ مهم
Local anesthetic action	Present	absent

[2] Weight: all drug doses are calculated according to body weight (mg/kg)

1-According to Chemistry:

Catecholamines	Non-catecholamine
- Contain catechol nucleus	-Don't contain catechol nucleus
- Not absorbed orally	-Well absorbed orally
-Rapid onset, short duration	-Slow onset, long duration
- can not pass BBB	can pass BBB
- Metbolized by MAO and COMT.	- Not metabolized by MAO or COMT
-Adrenaline, noradrenaline Dopamine, Isoprenaline, Dobutamine.	- Ephedrine, Amphetamine

تذكير أحنا هون ما عم نحكي عن metabolism انما عم نحكي عن response

3) Drugs Acting on Enzymes: drugs can modulate enzyme through:

- Activation of enzyme systems.
- Inhibition of enzyme:

أغلب الأدوية

ركزوا عليها

* مهم *- Neostigmine inhibit cholinesterase enzyme → increase Ach.

- Aspirin inhibits cyclooxygenase enzyme → decreases PGs synthesis

3- Aspirin inhibits PG synthesis برضو عمل تثبيط لل COX

- **Aspirin** – irreversibly blocks synthesis of cyclooxygenase
- **Indomethacin & Phenylbutazone** – reversibly blocks synthesis of cyclooxygenase.

IMPORTANT MICROSOMAL ENZYME INDUCERS (RBC)

مجموعة من الأدوية بتزود ال activity لل metabolism enzyme وبصير أعلى من الطبيعي فبتضل نسبة قليلة للعلاج بصير عندي loss of effect

- Barbiturates,
- Phenytoin
- Carbamazepine
- Rifampin
- Cigarette smoking
- Chronic alcoholism

Inducers

لما يكون المريض مدخن أو بيشرب كحول وما قلك ويصير عنده صداع وياخد دواء وما يجيب مفعول ويصير يحكي الدواء مو نافع بس ما بيعرف انه المشكلة جسمه بكسر بالدواء بسرعة فما بيستفيد منه

Examples of Enzyme Inducers

Phenytoin & carbamazepine- **ph**enobarbitone – **ri**fampicin - griseo**f**ulvin - ♂ androgen- nicotine- chronic alcohol ingestion.

لما تعرف ال drug على انو receptors بشتغل
بصير تتكلم عن الدوا من غير ما تذكرو بحيث
انت عارف وظيفته

- **Noradrenaline (NA)= Norepinephrine**

عشان نعا موجودة بستخدمها لما بدّل
الضغط لاني بوف انها بتقل

(α+weak B1+No β 2)

contraction

Therapeutic uses:

- **In hypotensive states to elevate BP.**

Receptor	Location	G Protein	Second Messenger	Major Functions
α_1	Effector tissues: smooth muscle, glands	G_q	↑ IP_3, DAG	↑ Ca^{2+}, causes contraction, secretion
α_2	Nerve endings, some smooth muscle	G_i	↓ cAMP	↓ Transmitter release, causes contraction
β_1	Cardiac muscle, juxtaglo-merular apparatus	G_s	↑ cAMP	↑ Heart rate, ↑ force; ↑ renin release

8- antiallergic action:

Adrenaline is the physiological antagonist of histamine.

* تكررت هذه المعلومة عدة مرات أثناء مادة الميد

حفظ

Examples of Enzyme Inhibitors

1 2 3 4 5
Cimetidine- **c**hloramphenicol - **c**iprofloxacin- erythromy**c**in - **k**etocenazol -

6 7 8
♀ **(F)** estrogen, progesterone, contraceptive pills.

anti-fungi

حبوب منع الحمل

Competitive Antagonist	Noncompetitive Antagonist
• Causes ***parallel shift to the right*** in the log dose-response curve i.e. ***No change in E_{max} but ↓↓ in potency (↑↑ in ED_{50})***	• Causes ***downward shift*** in the log dose-response curve with ***↓↓ in E_{max}***, ***but No change in potency (ED_{50})***

الدكتور قال رح يجي عليها سؤال بالامتحان

Redistribution of drugs :

* it means when you give a drug it is first distributed somewhere and then it is redistributed to somewhere else.
* this is seen with highly lipid soluble drugs such as thiopental , because these drugs cross the biological membrans easily.
* the drug first get distributed to organs with high blood supply (ex: brain, heart, kidney) and because they are lipid soluble they diffuse back and gets redistributed into less vascular but more bulky organs (ex: muscles and adipose tissue)

Streptomycin always ionized in any part of the body (Acidic or basic media)

3) From which of the following routes, bioavailability of the drug is likely to be 100 percent

A- subcutaneous

B- Intravenous

C- Intramuscular

D- Intradermal

and is advantage in case of large Volume

Elimination: metabolism + excretion

لما يكون ال drug شبه ال media ال absorbtion حيزيد و لو انعكس حيقل

d) Altered motility

Common

Metoclopramide (antiemitic)

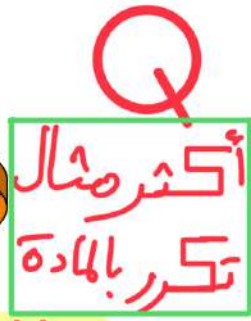
بقلل ال gastric empting بخلي المعدة تفضى ببطء يعني ال absorption رح يصير
بفترة أطول فبصير toxicity

Increase absorption of cyclosporine due to the increase of stomach empting time

Increase the toxicity of cyclosporine

Phenytoin is a highly bound to plasma protein (90%), and warfarin (99%)

بس 1% منه الي بيعطيني effect فلو زادت ال free عن 1% بتعمل bleeding



Drugs that displace these agents are **Aspirin**

warfarin الهم أقل من affinity **Sulfonamides**

مريض بياخد warfarin ممكن يصير معه صداع وياخد aspirin بالaspirin رح يفك ارتباط ال warfarin بال p.p. فبتزيد نسبة الfree تبعته ورح يسببلي bleeding

Uses:

1. PGE_1

-i.v to produce controlled hypotension. VD لأنه

-Intracavernous in cases of impotence. تربط ال VD بعطيهم اشي يعمل erectile dysfunction الناس يلي عندهم sex organs في ال blood flow

-Tried as vasodilator in peripheral vascular diseases.

-TGV. Transposition of great vessels
هاز congenital anomaly بكون فيه ال aorta مكان ال pulmonary والعكس؛ فبالتالي ال aorta بكون ماشي فيه ال non-oxygenated blood: فاهنا لما بنكتشف هاز الاشي ببداية الولادة بنعمل surgical treatment: بس مشان ما يموت الببي بكون فيه فتحة بين ال aorta & pulmonary بتسكر بعد اسبوع من الولادة بالوضع الطبيعي فاهنا
بنعطي دواء بخليها مفتوحة لحتى تنفذ شوي oxygenated blood in aorta مشان ما يموت الببي

-Misoprostol (cytotec) PGE_1 analogue used orally in peptic ulcers.
بتزيد ال mucus secretion و بتحمي المعدة من ال peptic ulcers

3-Epoprostenol (PGI_2) antiplatelet aggregation.

4PGE_2 tried in bronchial asthma but it is irritant.

5-PGE_2 & PGF_{2a} for induction of abortion and labor

6- PGs in Kidneys **increases GFR** and **promotes urine formation** → glomerular filtration rate
بكون محتاجة انزيد ال blood flow
and **urine out put.**Thus helps in **removing waste out of the body**. مشان اعمي الكلية

7-Latanoprost is PGF_{2a} used topically in treatment of glaucoma drainage of بزيد ال aqueous

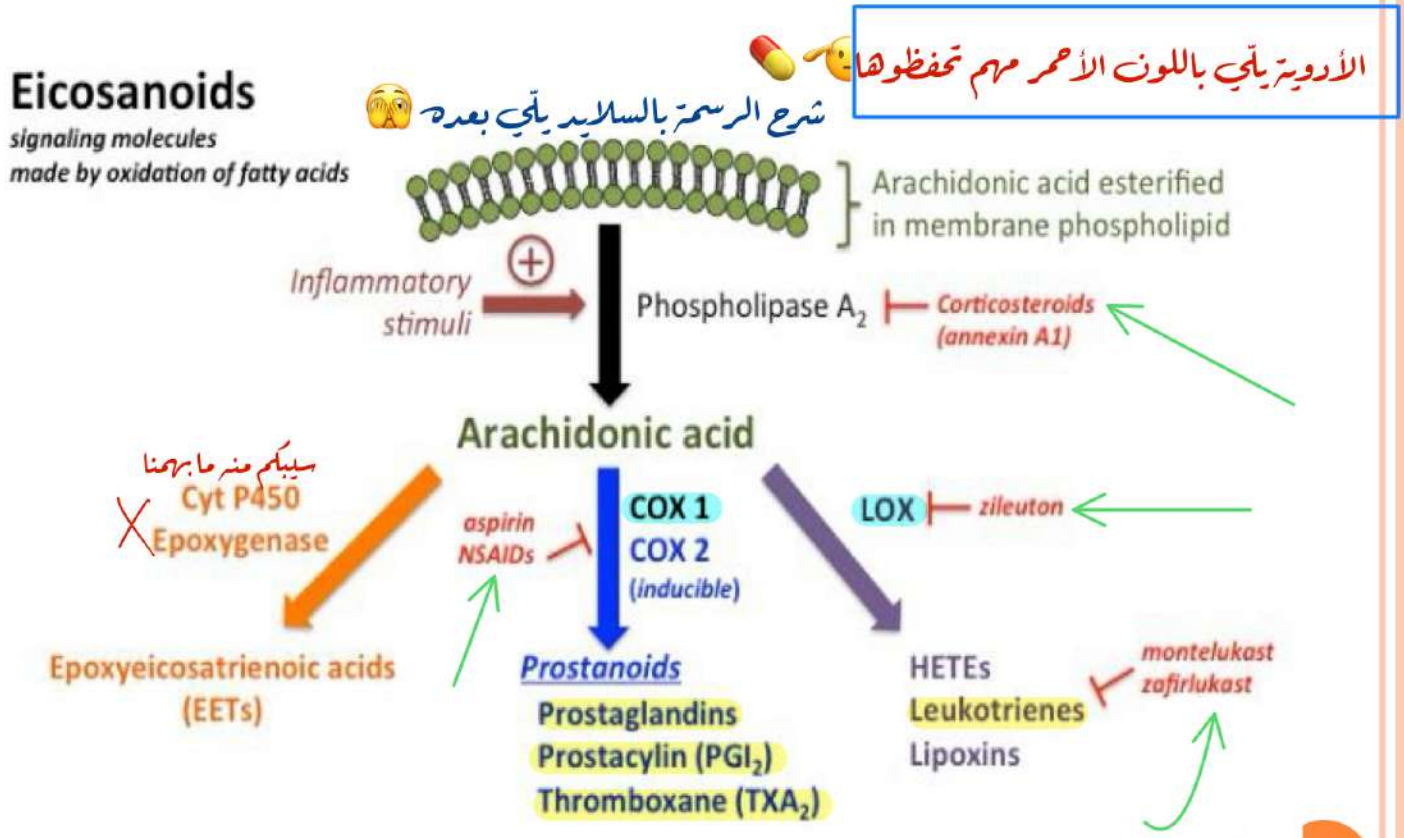
8-PGE2 is used in organ transplantation to reverse rejection

Indirect Parasympathomimetics (Anti-cholinesterases)

reversible or irreversible هاي الأدوية حسب طريقة ارتباطها في الإنزيم الي بكسر الأسيتيل كولين ممكن تكون

	Reversible	Irreversible
Binding to enzyme	loose يوقف بتركيه آخر شوي	Firm الارتباط قوي
Enzyme activity	Can be regained يوقف الانزيم يقدر يرجع لشغله بعد ماتركه	Can not
Action duration	short	Long
example	physostigmine, neostigmine, edrophonium مهمين حفظ	في المبيدات الحشرية ➢organophosphorus compounds Ecothiopate(antiglucoma drug) Malathion, parathion(antiscabes) Metrifonate(antihelminthic)

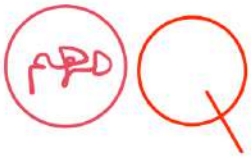
INHIBITION OF PG SYNTHESIS



- **Molecular mechanism o(muscarinic receptors stimulation:**
- 1- G - protein - coupling of $M_1 - M_3$ to phospholipase C , leading to the release of second messengers, Diacylglycerol (DAG) and Inositol triphosphate (IP3) .
- a- DAG modulates the action of protein kinase C , an enzyme important in secretion.
- b- IP3 evokes the release of calcium from intracellular storage sites,
- resulting in contraction of smooth muscles.
- 2- Coupling ofM2 to adenyle cyclase through the inhibitory G- protein.
- 3- Coupling of muscarenic receptors directly to potassium channels in the heart and elsewhere . Muscarenic agonists facilitate opening of these channels

When muscarinic receptors are activated in the heart and other areas of the body, they are influenced by muscarinic agonists, which facilitate the opening of potassium channels associated with them. This leads to an increased flow of potassium out of the cell and inhibition of the electrical activity of the cells, .resulting in the suppression of heart activity and a decrease in heart rate

Ex.,Erythromycin inhibit metabolism of ***astemazole and terfenadine***



Increase the serum conc.
of the antihistaminic leading to
increasing the life threatening
cardiotoxicity

Non Catacholamines

حكمة كل قروب نحفظ منه مثال

إن عليهم هايلايت حكمت محمين

CNS stimulant: as **Ephidrine** - **Amphetamine**

تثبيط الشهية ***Anorexigenices***: as Fenfluramine- Phenmetrazine

- ***Vassopressors*** as Methoxamine – Midodrine – Metraminol-
- **Phenyl ephrine (weaker than NA)**

Nasal decongestant **Old group: as Phenylephirine – Pseudoephedrine**

Recent group:as Naphazoline – Xylometazoline

Vasodilators and uterine relaxants as Isoxsuprine- **Ritodrine**

Bronchodilators as Salbutamol- Terbutaline- Salmiterol

Metabolism

SOME IMPORTANT INHIBITORS OF METABOLISM OF MULTIPLE DRUGS:

اول ما نحكي metabolism لازم يخطر ببالنا ال Cp450 "هو انزيم بس في ادوية بتحفزه كتير وبتخليه يكسرها بزيادة وفي ادوية بتثبطه وما بتخليه يكسرها بالشكل المطلوب"

- Macrolide antibiotics,
- Azole antifungals,
- Chloramphenicol,
- Omeprazole, SSRIs,
- HIV -protease inhibitors,
- Cimetidine,
- Quinolones (Ciprofloxacin)
- Metronidazole. (felagen)

} antibiotic

inhibitors

Treatment of anaphylactic shock

Epinephrine- hydrocortisone - antihistamines.

Physiological antagonist of histamine

Cardio selective beta blockers
selective beta1 blockers

- -ATENOLOL
- -METOPROLOL
- ~~-BISOPROLOL~~
- -ESMOLOL
- -ACEBUTOLOL

- **Uses**:Nicotine lozyenges are used in treatment of addiction of cigarette smoking .They maintain long standing minimal concentration of nicotine in plasma that prevent symptoms of nicotine withdrawal.now replaced by **Varneclin**

SIDE EFFECTS

- Unwanted often unavoidable Pharmaco-dynamic effects(not harmful). → (sleep not harmful) → (ال side effect لدواء الحساسية مثلاً)
- Occur at therapeutic doses.
- Predictable

Examples.

الدكتورة حكت أنه مرض وهو الوحيد اللي قرأته من الأمثلة

بس حاد المثال

-H1 Anti-histaminics- Sedation

سؤال مهم جدا

*** blood pressure:** β-blockers decrease the blood pressure through:

1. Decrease C.O.P — قللت ال cardiac properties ف ال bump صار ضعيف مش قوى
2. Inhibitin of renin release. — ال renin بعمل VC بالتالي بزيد ال bp
3. Resetting of baroreceptors. — البيتا بلوكر بتعمللهااعادة اعداد(يصير استشعارها لارتفاع ضغط الدم more sensitive)كيف؟تبدأ تتصرف لما يبقى الارتفاع دوت اقل من 30 يعني مارح استنى لازيد 30 حتى اتصرف
4. Presynaptic β2-blockade decreases NE release.
5. Central inhibition of sympathetic outflow.
6. Modulation of prostaglandin synthesis in favor of the vasodilator ones as prostacycline

صالح

لما بتطلع بتعمل

c) Drug-induced mucosal damage.

مريض اخد دواء يستخدم في chemotherapy (cancer treatment) هاد الدواء عمل damage لل mucosal (المكان الي بصير فيه ال absorption) ف صار مو نافع يعني صار not absorped

Antineoplastic agents

e.g., cyclophosphamide

~~vincristine~~

~~procarbazine~~

بيجي مريض وهو بيتعالج باستخدام ال cyclophosphamide ف الي بصير انه عمل damage لل mucosal وهو بياخد ال digoxin فبيجيك ويقلك ما نفع معي الدواء

Inhibit absorption of several drugs eg., digoxin

تجميعة القوانين (1)

- Bioavailability = $\frac{\text{AUC of adminstration}}{\text{AUC of IV}} \times 100$
- Vd = $\frac{\text{Amount of drug in the body}}{\text{Plasma concentration (Cp)}}$
- Total amount of drug = Vd x C_p
- Loading dose$_{IV}$ = Vd x Css
- Loading dose$_{oral}$ = $\frac{Vd \times Css}{F \text{ (fraction of oral bioavailability)}}$
- infusion rate = Clearance x Css
- Clearance = $\frac{.7 \times Vd}{t1/2}$
- Dosage rate = Clearance x Css
- MD_{IV} = Cls x Css x Timing
- MD_{oral} = $\frac{Cls \times Css \times Timing}{F}$

Needs receptors: either plasma membrane (1) or intracellular binding protein (2).

- **Eicosanoids** is a Generic term for the 20 Carbon related compounds like:

I. **Prostaglandins (PGs)** (الأهم)
II. **Prostacyclins (PGI2)** ← يعتبر نوع من ال PGs
III. **Thromboxanes (TX)**
IV. **Leukotrienes (LT)**
V. **Lipoxins (LX)**

لازم تحفظ الاختصارات

p80

1. Acetylation Polymorphism:

Genetic a bnormalties (idiosyncrasy):

- People can be classified according their rate of acetylation reaction in liver into **Rapid** and **Slow** acetylators

- Examples, in slow acetylators:

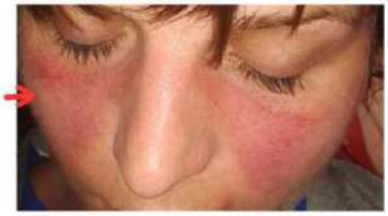
يستخدم في علاج TB.

a. **Isoniazid** → peripheral neuropathy (due to interference with pyridoxine (vit B6) metabolism).

هو يحافظ على وظيفة NS

b. **Hydralazine** → SLE-like (systemic lupus erythematosus-like).

مرض الذئبة الحمراء



vasodilator

SLE أعراض مشابهة لـ ← in this disease, the immune starts attacking body tissues

- Examples in rapid acetylators:

a. **Isoniazid** → hepatocellular necrosis (due to accumulation of toxic metabolites)

Consequences of drug interactions

1) **Loss of therapeutic effect** بكون ما حكالك انه بياخد دواء.. فبيرجعلك بعد فترة وبقلك ما استفدت

2) **Toxicity** بكون السبب اما خربطة منك او المريض بياخد ادوية ما حكالك عنها

3) **Unexpected increase in pharmacological activity**

4) **Beneficial effects e.g additive & potentiation (intended) or antagonism (unintended).** مقصودة

5) **Chemical or physical interaction e.g I.V incompatibility in fluid or syringes** عدم التوافق **mixture.** لما يصير interaction بين دوائين اثناء التحضير أو انت خلطت اكتر من دواء بنفس الإبرة... فاتغيرت خصائص الدوا بشكل كبير وصار loss effect

Classification of ADR

A (Augmented) B (Bizarre)

Broadly مقصود

Type- A (Predictable)- Based on pharmacological properties

Type- B (Non-predictable) – Based on Immunological response and genetic makeup of person