بسم الله الرحمن الرحيم

فيه نقطة احب انبه عليها في المذكرة

الاولى من الادرينيرجك

في صفحة 8 راح تلاقون ان النون .. بأكتب بالانقليزي

non catechol is

phenylepinephrine
epinephrine

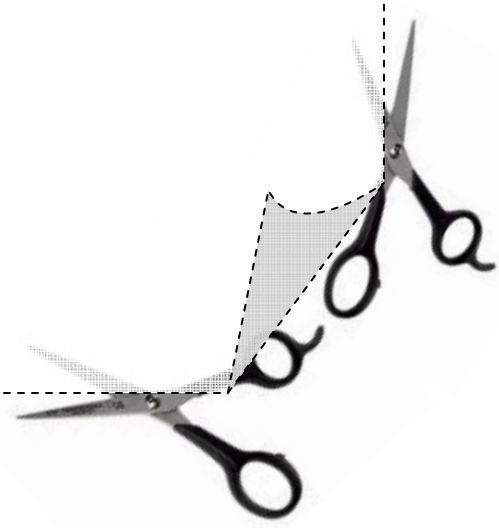
والصح هو

phenylephrine
and ephidrine

طبعا بعدين في المذكرة الثانية
راح الاقي ان الافدرين له ديريفاتفز
هذول يعدون كمان نون كاتيكول

والقادم اعظم ☺

لا تحرمونا من دعائكم



PharmPill team

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اللهم طهر قلبي من النفاق وعملي من الرياء ولساني من الكذب وعيني من الخيانة فأنت تعلم خائنة الأعين وما تخفي الصدور

اللهم اهدني لأحسن الأعمال والأخلاق ..

اخواني الطلاب .. اخواتي الطالبات دفعة 426

نحن فارم بل تيم قمنا بجمع مذكرات البنات مع الأولاد في هذه المذكرة
مع إضافة نوتات هذا العام
نسأل الله أن تنفعنا واياكم ... وتعود بالنفع لغيرنا
ان اصبنا فمن الله وان اخطانا فمنا ومن الشيطان

"اوجة شكر خالص الى الاخت دعاء البلوي دفعة 424 "

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Adrenergic Antagonists

Classification of Adrenoreceptor Antagonists :

- **α– BLOCKERS**
  - Non selective .
  - Relatively selective .
  - Selective .
- **β– BLOCKERS**
  - Non selective .
  - Relatively selective .
  - Selective .
- **BOTH α AND β ADRENERGIC ANTAGONISTS**

1- α- Adrenoceptor Antagonists (α- blockers) :

- **NON SELECTIVE**
  - Phenoxy benzamine
  - Phentolamine
  - Tolazoline
- **RELATIVELY SELECTIVE α_1**
  - Prazosin
  - Terazosin and Doxazosin
- **RELATIVELY SELECTIVE α_2**
  - Yohimbine
  - Idazoxan
- **SELECTIVE**
  - Tamsolusin .

NOTE :

- Selectivity for α– receptors explain why these agents produce less reflex tachycardia than do nonselective α– Antagonists
-
  - ✓ e.g. phentolamine blocks both presynaptic and postsynaptic α–receptors result in reflex stimulation of sympathetic neurons produces greater release of transmitter onto β–receptors and correspondingly greater cardioacceleration (called reflex tachyardia). there is another cause for reflex tachycardia see below .

Actions of α– blockers : (in general)

- α– blockers reduce arterial pressure by dilating both resistence and capacitance.
- As expected , BP is reduced more in the standing than supine position because of dilation of veins in the lower part of the body which cause fall of blood in the lower part and poor supply to blood in the brain (Postural hypotension) .
- These drugs are more effective when it used in combination with other agents , such as β–blockers and a diuretic , than when used alone .

a. Non selective α– blockers :

Note before going to details : Although they have limited clinical applications, the non-selective α– blockers, are very important for understaning the autonomic nervous system.

Their use is limited because they cause two antagonising effects on blood pressure when working on α_1 and α_2 receptor simultaneously:

1. ***When α_1 is inhibited, there will be vasodilatation and decrease in B.P***
2. ***But when α_2 is inhibited, NE release will not be inhibited so it will increase and casue vasoconstriction and subsequent increase in BP.***

❖ Mechanism of actions :

• Phentolamine and Tolazoline (Reversible) :

- Induce reversible competitive blockade for α_1 and α_2– adrenoreceptors which can be overcome by increase of NE
- T1/2 = 3 – 5 hours (short acting)

• Phenoxybenzamine (Irreversible) :

- It alkylates the receptors & binds by methyl covalent bond. Thus, it produces irreversible noncompetitive blocks for both α1 (postsynaptic) and α_2 (presynaptic) adrenoceptor which cannot be overcome by increase of NE . it also block the action of histamine, Ach, and serotonin.
- **$T_{1/2}$ = 14 – 48 hours (long acting)**

❖ Pharmacological effects of α– blockers :

I. Effects Mediated by blocking α–receptors :

A. Cardiovascular Effects:

1) **They block** :

- α1 causing VD. So, decrease TVR
- The pressor effect of α– agonists So, they decrease BP (hypotension) .
- But they are of limited clinical use in treating hypertension because they may cause:
    - Tachycardia (Reflex Type)
    - Cardiac arrhythmia
    - Angina pectoris
    - Peptic ulcer
    - Sexual dysfunction
    - Postural hypotension.

2) They produce tachycardia more than the α_1 – selective blockers by :

- **Producing reflex tachycardia:**
    - All α blocker (selective and non selective) block α_1 to inhibit the effect of sympathetic tone on blood vessels. This lead to VD & decrease BP (more obvious during standing) leading to postural hypotension. This will stimulate the baroreceptors to send impulses to CNS to increase HR (tachycardia)

- **Increase HR by :**
    - Block α2 cause increase NE in synapse. This will increase HR
    - (this effect does not happen in selective α1 blocker only)

N.B: the block of α2 adrenoceptors increase n noradrenalin release which make the drug unsuccessful in maintaining lowered BP

- **Phenoxy benzamine :**
    - Block NE reuptake. This will increase NE in synapse leading to increase HR. So, more tachycardia with Phenoxybenzamine as compared to phentolamine.

- **Produce Adrenaline reversal**
  - Normally : EP stimulates α_1 to cause general VC & increase BP and also stimulate β_2 to cause VD in skeletal muscle, but this effect is masked by α_1 vasoconstrictor effect. So, the net result is **increased BP**. If α_1 – receptors are blocked by α– blocker, only the β_2 vasodilator effect will appear upon stimulation by EP. So, vasodilatation and decrease BP will occur. This case of decreased BP upon adrenaline stimulation is called adrenaline reversal .

B. Non-cardiac Effects of α– blockers :

a) Miosis **(done by inhibition of radial muscle contraction)**
b) Nasal Stuffness.
c) Decrease resistance to the flow of urine
d) They decrease adrenergic sweating. So, they produce dry skin .
e) They decrease the ability for ejaculation.

II. Effects mediated by non- α–adrenergic blocking effects:

They induce weak blockade for:

- H1 receptors (Histamine) (Sedation; GIT)
- Serotonin receptors
- Muscarinic receptors (dry mouth)

❖ Side effects of Phenoxybenzamine :

- **Postural hypotension**
- **Tachycardia**
- **Nasal stuffiness**
- **Inhibition of ejaculation**
- **Fatigue**
- **Sedation**
- **Nausea**
- **Diarrhea**
- **Vomiting**
- **impotence**

❖ Side effect of phentolamine :

- As phenoxybenzamine but more to induce cardiac arrhythmias and anginal pain, both are contraindicated in patients with decreased coronary perfusion.

b. α_1– blockers relatively selective :

◙ Note:

Drugs end with "-azosins" are all α_1 blockers, and they used in treatment of hypertension.

1- PRAZOSIN :

❖ Mechanism of action :

- It is a relatively selective α_1 – adrenoceptor competitive antagonist
- It's action can be overcome by increasing agonist concentration
- **Its short acting** , T1/2 **: about 3 hours**

❖ Actions :

- It produces **arterial & venous dilation**. So it decreases BP, so it is used for the treatment of hypertension
- It causes **less tachycardia** than non–selective vasodilators Why?

Because NE will not be able to stimulate a1 receptors which is blocked and will be forced to stimulate a_2 which causes a –ve feed back mechanism by decreasing the release of NE therefore decreasing the activity of NE on the heart consequently decreasing tachycardia which is normally produced by NE stimulation.

In brief :
Because they don't increase noradrenalin release from sympathetic nerve terminal.

- It precipitates less angina & cardiac arrhythmia
- It may **increase HDL / cholesterol ratio**. HDL protects against ischaemic heart disease **(good effect) .**
- There is tolerance to it's action .
- **Decreases preload and after load of the heart --- therefore used for Congestive heart failur.**
- **Because it's metabolized by the liver , only 50% of the drug is available after oral administration .**
- Dose 2 – 3 times daily for **Hypertension** and **Congestive heart failur** ?.

❖ **Side effects :**

- 1st dose produce hypotension & syncope, but this disappears after continuous treatment .

How could you limit this side effect?
1- start treatment with low doses.
2- give the doses at night.
3- ask the patient not to stand or walk immediately after prazosin administration.

- Infrequent postural hypotension (rare and less than the non selective) .
- Nasal stuffiness due to VD & congestion .
- Dizziness, headache & faintness . These are caused by hypotension .
- Sexual dysfunction but less than the non-selective.

2-Terazosin & Doazosin :

- They are relatively α_1 – selective blockers, with higher selectivity than prazosin
- T1/2 = Terazosin 12 hours; Doxazosin 22 hrs allowing once daily dosing, while prazosin 3 hr. only!!
- They produce VD with less tachycardia than prazosin
- Like prazosin it produces postural hypotension
- They produce relaxation of smooth muscle of the bladder neck and prostate capsule. So, they **facilitate micturition**. For this action, they can be used in case of urine retention associated with benign prostatic hyperplasia- BPH- in which prostate compresses the urethra & prevent micturition.

c. α2– blockers relatively selective :

- **yohimbine** is a natural alkaloid, **Idazoxan** is a synthetic drug.

✓ (α_2 receptor agonists inhibit insulin secretion ,so these drugs are used in the treatment of diabetes)
✓ They are used in the treatment of peripheral vascular disease
✓ Used in the treatment of psychiatric depression.

d. α– blockers Selective :

TAMSOLUSIN:

❖ Introduction :

- It is selective for α_1A – adrenoreceptors in the sphincter of urinary bladder
- T1/2 : 9-15 hours .
- Metabolized extensively in the liver .
- α_1A stimulation leads to contraction of the sphincter. So, no micturition .
- α_1A blockade leads to relaxation of the sphincter. So, it facilitates micturition .
- Tamsolusin is used clinically in treating urine retention associated with BPH. It is better here than prazosin, Terazosin and Doxazosin.
- It causes less hypotension than prazosin or terazosin. Because:
- It has low potency in inhibiting receptors in vascular smooth muscle.

❖ Adverse affects :

- Retrograde ejaculation 15%
- Hypersensitivity reaction: skin rash & urticaria
- Nausea and vomiting
- Nasal obstruction
- Over dose will cause hypotension, tachycardia and fatigue
- **It may increase erection.**

Note: Similar to prazosin but with less magnitude.

❖ Contraindications :

- Renal impairment :

- Tamsolusin is metabolized in the liver to an active metablite which is entirely excreted via the renal tubules, therefore,
- In case of renal impairment, Tamsolusin will accumulate in blood & lead to toxicity .

Clinical Uses of adrenergic α-antagonists:

1) Pheochromocytoma **(phentolamine, phenoxybenzamine)** but not alone Why?
Because it may cause very strong tachycardia having diverted the NE and EP from the blocked α receptors to the free β1 receptors and activating it.

2) Hypertensive Crisis **(Labetalol).**

3) Essential Hypertension **(Prazosin, Terasozin).**

4) Peripheral Vascular Occlusion Diseases .(Raynoud's phenomenon) e.g: **Prazosin, phentolaime, and phenoxybenzamine** but Calcium Channel Blockers are better choice) .

5) Urinary Obstruction BBH **(Tamsolusin)** .

6) autonomic hyperflexia which lead to paraplegia,and stroke **(phentolamine and phenoxybenzamine).**

2- Adrenoreceptor Antagonists (β- blockers):

- **NON SELECTIVE :**
  - Propranolol
  - Timolol
  - Nadolol
  - Labetalol
  - Pindolol

- **RELATIVELY SELECTIVE** (Cardioselective) (on β_1) :
  - Atenolol
  - Esmolol
  - Metoprolol
  - Practolol
  - Acebutolol
  - Bisoprolol

- β- ANTAGONISM + α- ANTAGONISM
  - Carvedilol
  - Labetolol

How could you distinguish between β -adrenergic Blockers?

- **β- adrenergic antagonists (blockers) differ from each others in the following:**

- Selectivity for β_1 as compared to β_2.
- Some of them like (pindolol; acebutolol) have partial agonistic activity.
- Some of them have local anesthetic or the so-called membrane stabilizing action (propranolol; pindolol; acebutolol) except **timolol** .
- Some of them metabolized in the liver (propranolol; pindolol and Timilol) while others (like Atenolol and Nadolol) eleminated in the Kidney.

❖ Pharmacokinatic of β blockers :

- **Absorption :**
  - ✓ Most of them are well absorbed orally. Sustained-release (slow-release) preparations of propranolol and metaprolol are available

- **Bioavailability :**
  - ✓ Propranolol undergoes extensive first pass hepatic metabolism (bioavailability is low).
  - ✓ Most of them have limited bioavailability with the exception of pindolol, sotalol and betaxolol (90%) high bioavailability.

- **Distribution and clearance :**
  - ✓ They are rapidly distributed, propranolol and penbutolol cross readily BBB. Most of them have a half-life from 3-10 hrs except esmolol (10 min).
  - ✓ most of them metabolized in the liver and excreted in urine.
  - ✓ Nadolol is excreted unchanged and has the longest half-life 24 hrs.
  - ✓ the elimination of propranolol is affected by liver disease.

❖ Pharmacological actions :

A. CVS :

In brief :
- **Bradycardia**
- **Hypotension**
- **Peripheral vasodilatation**

BP = CO X TVR. Clinically β blockers lower BP By these mechanisms:

1) Cardiac Mechanism :
- Having both –ve inotropic and chronotropic effect.
- Blockade of β_1 in the heart will cause decreased HR and CO and finally BP will be decreased.
- **Mere decrease of CO does not explain the decrease in BP because after 2-3 weeks, the CO will return to normal but the BP will remain low.**

2) Renal Mechanism :

- Blockade β_1 in the kidney will decrease renin leading to a decrease in angiotensin II. this will result in:
    - VD and ultimately decreased BP
    - decrease aldosterone. This will lead to decreased salt and water retention and finally decreased BP
    - decrease release of NE that will cause VD and decreased BP .

◙ **Note:**

- Elderly and black people have high level of renin, so β blockers won't affect the renin level.
- **Carvedilol,** and **Labetolol** have extra α blocking effect and peripheral vasodilation through NO, this will cause postural hypotension.

3) CNS Mechanism :

- Blockade of central β adrenergic in adrenergic nerve terminals. This will makes NE acts at α_2-adrenergic leading to a decrease in its own release and decrease sympathetic tone to blood vessels, leading to VD and decreased BP

Which one of the above THREE mechanisms is more important to explain the hypotensive effect of β -adrenergic Blockers?

- **The renal mechanism.**

B. The respiratory system (Unwanted Effects) :

- Blockade of β_2 receptors in bronchi will cause bronchoconstriction
- Non–selective β blockers (are contraindicated in the bronchial asthma and COPD [chronic obstructive pulmonary disease] (propranolol)
- The β_1 selective blockers (e.g: Atenolol; Bisoprolol) are also **should be used with caution** in the bronchial asthma because their selectivity is **relative** and they may have antagonistic affects on the β2 receptors at therapeutic doses.

C. The eye :

- **β–blockers are used in treatment of glaucoma (Timolol). They act by:**
  - Blocking β_2 in ciliary epithelium. This will decrease production of aqueous humor and will decrease intraorbital pressure (IOP) e.g., timolol
  - Block β_2 in ciliary muscle. This will cause contraction of the ciliary muscle leading to Opening of the canal of Schlemm, this increases outflow of aqueous humor which leads to Decreased IOP (in the open- angle glaucoma) .

D. Metabolic and endocrine effects:

- Glycogenolysis in liver is inhibited by (β_2 – blockes) and ↓ glucagon secretion.
- Increased Na retention
- Decrease in BP causing decrease in renal prefusion.
- β blockers impair sympathetically – induced lipolysis (propranolol inhibits lipolysis), however,
- Chronic use of β – blockes causes increase **VLDL** & **TGs** and decrease **HDL/ Cholesterol** ratio. So, they will :
  - Increase risk of coronary artery disease
  - contraindicated in a patients with familial hypercholesterolemia because VLDL & TGs are atherogenic & may cause myocardial infarction
  - **This information is not practically right.**
  - **In fact, people with MI should be given β_1 antagoinst to decrease the infarct size and limit the myocarial demand for O2 and nutrients.**

Note:
This effect occurs with both the selective and non-selective β-blockers, but less with β-blockers with intrinsic sympathomimetic activity (partial agonist e.g: Pindolol) .

- **In insulin – dependant diabetics (type 1).**
  - β blockers mask the symptoms of hypoglycemia (sweating, tachycardia, tremors). So, the symptoms indicating hypoglycemia are absent because these symptoms are mediated by NE effects in HR and once it is blocked the signs for hypoglycemia will be absent leaving the body suffers from it without interference. For this reason, the patient should measure the blood glucose level after each insulin injection.

Note: Non selective β- blockers (propranolol) should be avoided if patients is insulin dependent diabetic.

- **What about Type 2 diabetes mellitus patients?**

there is no effects of B blockers because the patient normally has a high blood glucose level so he rarely shows signs of hypoglycemia even immediately after insuline injection .

E. Intrinsic sympathomimetic activity (ISA) :

- Some of the β- antagonist produce some action as β- agonist e.g. **Pindolol; Acebutolol & Labetalol**, so, they are less dangerous when given to patients with bronchial asthma or excessive bradycardia .

F. Membrane Stabilizing Action (MSA) :

- Some β- blockers stabilize the cell membrane by blocking Na^+ channels. Therefore, produce "local anesthetic action" e.g**. Propranolol not pindlol.**

G. Class III anti arrhythmic effects :

- **Sotalol** acts as potassium channel blocker**.**

So What?

Solatol will block the exit of K^+ causing hyperpolarization which decreases the heart rate and causes re-organization of the cardiac rhythm.

Non-selective β– blockers

1. Propranolol (Indral^{R})

- It is a non–selective β blocker
- It is Lipid soluble (CNS)
- It undergoes extensive first–pass hepatic metabolism (90% of the drug). Short t1/2 (2– 5 h).
- Can be given orally or I.V
- It is excreted in urine mainly as Glucouronide conjugate
- It's duration of action is increased in :
  - ✓ Hepatic disease
  - ✓ Decreased hepatic BF
  - ✓ Metabolic inhibition e.g. when giving Cimetidine, it inhibits the metabolism of propranolol, Thus , prolonges T1/2
- It has **no ISA**
- It has **MSA**
- It is used as antiarrhythmic drug
- It stabilizes the cardiac cell membrane & decrease the activity of ectopic foci

2. Timolol:

- Like propranolol, It is non–selective β blocker.
- T1/2 = 4 – 5 h
- No ISA
- No MSA
- Lipid – soluble
- Note: PK similar to propranolol
- Pass via the cornea. So, it is used as eye – drops to treat glaucoma

3. Pindolol:

- It is non selective β blocker
- T1/2 = 3 – 4 h (liver)
- Has ISA or so-called partial agonistic activity (important for Asthma; CHF)
- Lipophilic but less than propranolol
- Has MSA but less than Propranolol
- Pindolol and acebutolol are affective in hypertensive patients with moderate bradycardia
- Carbohydrate metabolism is less affected with acebutolol and pindolol than with propranolol, making them valuable in treatment of diabetic.
- What is the benefit of Intrinsic sympathomimetic activity?
  - ✓ Less cardiac depression
  - ✓ less bronchospasm
  - ✓ Minimize the disturbances of lipid by traditional β-blockers.

4. Nadolol

- This drug differs from the other three b-blocker n the following:
- It is not lipid soluble
- It mainly eliminated by the kidney and has longest t1/2 among most all β-blockers (12-24 Hr)
- Due to the above, it has no ISA or MSA.
- Eliminated by kidney .
- Longer duration .
- Use for esophageal varices .

Selective β– blockers (Cardioselective β– blockers)

1. Atenolol (Tenormin®):

- Note: It is a **relative** β1 selective blocker
- It is water soluble, so, it has
  - ✓ Longer t1/2 = 12 – 18 h because it stays in tissue for a long time
    - For this reason, the dose is once daily
- Less severe side effects on CNS because it is not lipophilic like propranolol
- No ISA
- No MSA
- Adverse effects include :
  - ✓ Impairment of glucose tolerance
  - ✓ Bradycardia
  - ✓ Bronchospasm less than non-selective
  - ✓ Sexual dysfunction
  - ✓ Fatigue : due to decreased blood supply to the periphery (less than propranolol)
  - ✓ (Exercise intolerance)

2. Bisoprolol (Concor®):

- Selective blocker, with very high oral bioavailability as compared to Atenolol (80% VR 40%, recpectively)
- Potent as compared to Atenolol (MCQ) (5 mg VR 100 mg, respectively)
- Like Atenolol, it is water-soluble with long duration of action.
- Uses: Like Atenolol (HTN; Ischemic Heart Diseases; Arial fibrillation and CHF)

3. Metoprolol

- It is a relatively β_1 – selective blocker
- But, like proranolol is metabolized in the liver (short t1/2)
- It is not used to treat hypertension because of it's side effect

4. Esmolol : (antiarrythmic drug)

- It is a selective β_1 – blocker
- Since it is an ester, it has very short duration of action (T1/2 = 8-10 min) (esterase in RBC)
- It is given I.V when short – term β blockade is required
- It is used in critically – ill patients (e.g.supraventricular arrhythmia) in whom the adverse effects of bradycardia or heart failure may require stopping the treatment.
- It is used in emergency mainly during surgery in sudden arrythema (IV injection)

Note:
Acebutolol, atenolol, metoprolol, esmolol:

- ✓ They have little effect on pulmonary function, peripheral resistance, and carbohydrate metabolism.

Drugs that block both β-and α-adrenoceptors

1. Labetalol (has more effect on β)

- It is non – selective β blocker & selective α_1 blocker
- **Note: At small doses it blocks b-adrenoceptors only (1:3)**
- T1/2 = 4 – 6 h
- Weak lipid – soluble
- It has ISA
- No MSA
- It differs from other β blockers in that it produce tachycardia rather than bradycardia and less peripheral vasoconstriction.
- It blocks α_1 in blood vessels. So, causes VD and decrease BP (postural hypotension) , effective for treatment of hypertension in patient with increased peripheral vascular. This will stimulate baroreceptors to send impulses to CNS to increase HR (reflex tachycardia)(MCQ) **but this tachycardia is less than seen with other α blockers**

Clinical Uses:

- It is used in Pheochromocytoma
- Hypertension in pregnancy
- Hypertensive crisis
- Hypertensive emergencies as it is rapidly lowering BP

Adverse effect:

- Orthostatic hypotension and dizziness are associated with α1 blocker

2. Carvedilol :(more potent)

- It is non–selective β blocker and non – selective α blocker
- It can be used in patients with heart failure due to:
  - ✓ It is a peripheral vasodilator (independent of adrenoceptor blockade)
  - ✓ It has antioxidant activity
  - ✓ It can neutralize (scavenge) the free radicals which cause heart failure
- It used in renal impairment
- Because it improves kidney function. So, it used in patients with Renal impairment

- Drugs that block both β–and a-adrenoceptors do not greatly alter serum lipid or blood glucose level.

Therapeutic (clinical) uses of β– blockers :

Hypertension :
- Labetalol a competitive α , and β antagonist is effective in hypertension.
- β- blockers are less effective in blacks and the elderly people.

Ischemic heart disease :
- Reduce the frequency of anginal episode
- Improve exercise tolerance
- Decrease cardiac work and O_2 demand
- Reduce heart rate
- They are effective as prophylactic in myocardial infraction

Pheochromocytoma
- a functional chromaffinoma, usually benign, derived from adrenal medullary tissue cells and characterized by the secretion of catecholamines, resulting in hypertension, which may be paroxysmal and associated with attacks of palpitation, headache, nausea, dyspnea, anxiety, pallor, and profuse sweating. See Also: paraganglioma.
- (β-lockers or Labetalol)

Cardiac arrhythmias
- In the supraventricular and ventricular arrythmias
- Sotalol has ionic channels blockade in addition to its β-blockade effect.

Chronic heart failure (CHF)
- Metaprolol, bisoprolol and Carvidalol decrease myocardial remodeling and decrease the risk of sudden death.

Free radical cause remodeling, which cause failing heart. Carvidalol has an antioxidant activity that trap free radical .traping cause decrease in the remodeling

Obstructive cardiomyopathy
- (Decrease out flow resistance)

Dissecting aortic aneurysm
- (Decrease systolic pressure)

Atrial Fibrillation
- (Atenolol; Bisoprolol)

Post MI
- (Atenolol; Bis)

Glaucoma
- Decrease IOP through decrease the production of aqueous humor by the ciliary body, which is activated by cAMP
- Timolol (given topically) and related β-antagonists are suitable for local use in the eye because they lack local anaesthetic properties
- Systemic timolol may be absorbed from the eye to cause serious adverse effects on the heart and air ways.
- Topical timolol may interact with orally administrated verapamil (antihypertensive) and increase the risk of heart block.
- Betaxolol, cartelol are newer β-antagonist used mainly for treatment of glaucoma.
    - ✓ Betaxolol is a selective β_1 antagonist has less systemic adverse effects (lung, GIT, carbohydrates, lipid)

Hyperthyroidism
A] to diminish catecholamine action which play an important part of the pathophyisology of the disease .
B] inhibit the peripheral conversion of thyroxine to triiodothyronine, e.g., propranolol is used in sever cases to control supraventricular tachycardia that precipitate heart failure.

Neurogical disease
- Propranolol in migraine and headache.
- Metaprolol, atenolol, nadolol can be use also.
- To reduce certain type of tremors (Atenolol; propranolol)
- To reduce anxiety (propranolol)
- Propranolol may used in symptomatic treatment of alcohol withdrawal

Miscellaneous
- To diminish portal vein pressure in hepatic cirrhosis (nadolol)
- Propranolol and nadolol decrease bleeding from oesophageal varices and mortality rate.

Adverse effect and toxicity of β adrenergic receptor antagonists :

- Rash, fever – drug allergy
- CNS include : Sedation and Depression and sleep disturbances [These are more sever in Lipid soluble β blockers (e.g. Propranolol) than in water soluble β blocker (e.g. Atenolol)]
- Worsening Asthma (due to b2-blockade); however, can be used with caution for patients with H/O Asthma.
- Same as for asthma in peripheral cardiovascular diseases.
- Easy fatigability
- Exercise intolerance
- Impotence
- In patient with abnormal myocardial function, or cardiac output depend mainly on sympathetic effect. So β-blockade cause cardiac decompensation. A life-threatening adverse cardiac effect of a β-antagonist can be overcome by isoprotenol or glucagon.
- With verapamil lead to sever hypotension, bradycardia, heart failure (topical β-blockers and oral verapamil)
- Sudden withdrawal of β antagonist can cause sever cardiac risk in ischemic heart disease (gradual withdrawal is very important)
- Hypoglycemia

- Which of the β-blockers produce **cold extremities**?
- Which of the β -blockers produce **easy fatigability? (atenalol)**
- Which of the β -blockers produces **depression**?
- Do β -blockers give rise to postural hypotension? No , drugs that block both β–and a-adrenoceptors produce Postural hypotension .

Heart failure and β-blockers

- β- blockers may precipitate heart failure by causing negative ion tropic effect and bradycardia.
- However, new studies suggest that β- adrenergic blockers **should** be given to most patients with heart failure unless he is in stage 4 (Symptomatic).

Contraindications of β-blockers:

- Bronchial asthma (mainly the non-selective)
- Heart block (Bradycardia)
- Peripheral vascular disease (with the non-selective)
- Heart failure if severe only (relative).
- Type 1 D.M.(relative)

Drug interactions:

- **Verapamil** a Ca^{++} - channel blocker.

If it is combined with β – blockers, this can cause :

- ✓ Congestive heart failure
- ✓ Severe bradycardia
- ✓ Severe hypotension

- **Digoxin** (severe bradycardia)

Withdrawal of β- blockers:

- On chronic use, abrupt withdrawal of β – blockers causes the β receptors to become supersensitive and even the circulating catecholamine can stimulate them & cause severe arrhythmia. So, withdrawal should be very gradual over weeks.

✓ Note: This more common with short acting β-blockers like propranolol.

Centrally acting sympatholytic drugs

Methyldopa
Clonidine
Moxinodine

α– methyldopa

- Prodrug .
- Positive comp test .
- Causes decrease in dopamine .
- High dose (750 mg)

PK (pharmacokinatic)

- α– methyldopa is a prodrug given orally then absorbed from GIT & enters the circulation
- It freely passes BBB & reaches CNS then it is converted to α– methylenorepinephrine which acts as an agonist at central α2 – adrenoreceptors then It will decrease the sympathetic tone to blood vessels. So VD a decrease BP will result

Mechanism of action:

- The metabolite of α– methyldopa (α– methylenorepinephrine) will act as a false neurotransmiter and activites central presynaptic a2-adrenoceptors, leading to a decrease in the outflow of NE to the peripheral. This eventually decreases the vascular resistance and CO with a significant decrease in mean blood pressure.

Clinical uses:

- Treat pregnancy – associated hypertension
- Treat mild to moderate hypertension (not commonly used)
- Can also be used for Rx of refractory hypertension

Side effects include:

- It may produce orthostatic hypotension when standing from the sleeping position ,This not severe like α– blockers
- Sedation, insomnia, depression (cuz decrease nor epi) in the beginning of treatment & disappears after continuous use
- Serious extrapyramidal (parkinson) sings
- Methyldopa decrease the turnover of Dopamine and leads to extra- pyramidal side effect (Parkinson)
- Prolactin release (How?) (by decrease dopamine)Even in male : the breast may produce milk
- Hepatitis & drug fever (can be serious)
- Impotence
- A lupus – like reaction : skin rash and pustules
- Hemolytic anemia (+ve coomb's test)
- Leucopenia : sometimes

Clonidine:

- It is an imidazoline derivative and it is unlike methyldopa acts directly a an α_2 – agonist
- No decrease in dopamine .

Mechanism of action :

- Clonidine is Lipid – soluble, so, it freely passes BBB & reaches CNS to stimulate α_2 – receptors in medulla and pons causing to decreased sympathetic tone and finally decrease BP
- It acts by it self not like Methyldopa

Clinical use include:

- Treatment of mild to moderate hypertension
- Treatment of morphine withdrawal symptoms
- Hypertensive metabolic syndorme
- As analgesic during labour
- The dose = o.2-1.2 mg/day
- Why the dose of clonidine almost 100 times less than methyldopa? Because its direct acting drug (not prodrug).
- It can be given transdermally
- Clonidine produces severe rebound hypertension upon abrupt withdrawal

يرتفع الضغط جدا اعلى مما كان عليه قبل العلاج والحل هو ان ترجع العلاج

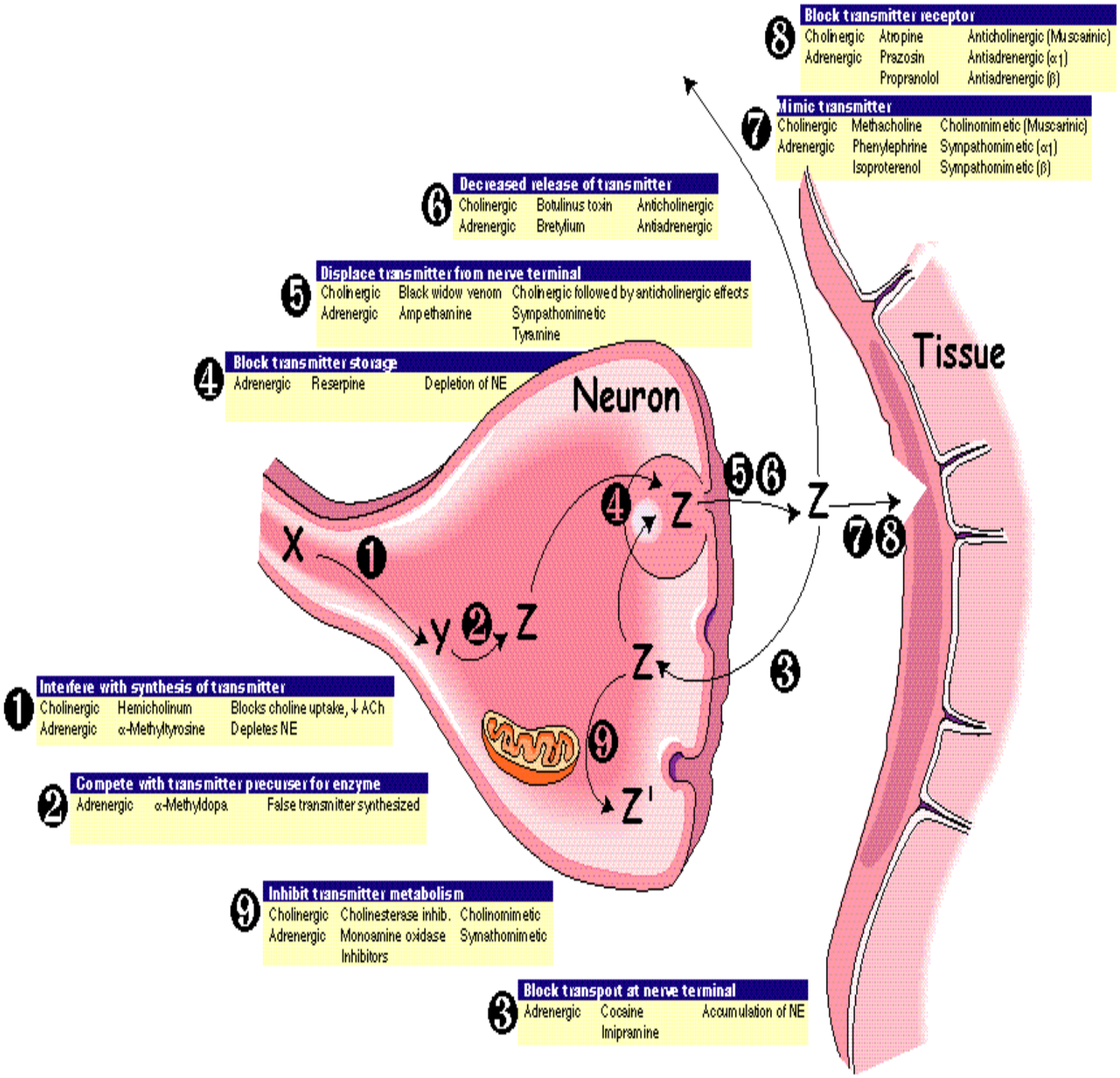
Adverse affects

- Dizziness, sedation, mental depression
- Impotence
- Alopecia تساقط الشعر
- Weight gain

✓ **Sudden withdrawal leads to rebound hypertension upon abrupt withdrawal**

✓ **What are the differences between clonidine and methyldopa? (revise both you will have a question on both)**

Drug affecting neurotransmitter release or uptake



Reserprine

- A plant alkaloid, blocks Mg +2/adenosine triphosphate (ATP)-dependant transport of biologic amines (norepinephrine, dopamine and serotonin from the cytoplasm into storage vesicles in the adrenergic nerves of all body tissue)
    - This result in depletion of norepinephrine levels in adrenergic neurons . MAO can degrade the nrepinephrine in the cytoplasm.
    - Hypertensive patients show a gradual decline in BP and HR.
- Reserpine has a slow onset and long duration of action
- It is used only to treat hypertension no respond to other treatment

Guanethidine

- Blocks the release of stored norepinephrine , this lead to gradual drop in BP and HR causes transient increase in BP. It is used in the treatment of hypertension.
- Adverse effect :

✓ Guanethidine causes orthostatic hypotension and male sexual dysfunction
✓ Supersensitivity to norepinephrine due to depletionof amine may result in hypertensive crises in patients with pheochromocytoma.

Cocaine (CNS stimulant)

- Has a local anaesthetic action by blocking Na/K activated ATPase required for cellular uptake of norepinephrine across the cell membrane of the adrenergic neuron.

revision

α-adrenoceptor agonists and antagonist clinical uses in general

❖ **General uses of α-adrenoceptor agonists**

- Bronchial asthma (acute, and chronic)
- Anaphlaxis
- Mydriatic (facilitate retina examination and as decongestant for minor allergic and itching in conjunctival membrane)
- Glaucoma (brimonidine a selective α2 agonist lower IOP)
- Terbutaline suppress premature labor

❖ **Common side effect of α-adrenoceptor antagonists**

- Impotence
- Reflex tachycardia
- Postural hypotension

❖ **General clinical uses of α-adrenoceptor antagonists**

- Hypertension, non-selective α-adrenoceptor antagonist drugs are unsatisfactory, because of their tendency to produce, tachycardia, cardiac arrhythmias, and increased GIT activity.
    - The long acting α1-adrenoceptor antagonists are preferred as doxazosin and terazosin. Less effect on cardiac function and less postural hypotension than short acting prazosin or with non selective α- blockers.
    - Peripheral vascular disease (Raynawd's)
    - Local vasoconstriction excess, phentolamine is used to reverse the intestine local vasoconstriction effect of norepinephrine. Phentolamine is given by local infiltration into the ischemic tissue.
- Benign prostatic hypertrophy, e.g., tamsulosin (selective α1A-adrenoceptor antagonists) to control urinary retension
- Pheochromocytoma together with β blockers
- Erectile dysfunction
    - Direct injection of phentolamine with papaverine into the penis may cause erection with sexual dysfunction.