



Artery Academy

Done by Hawazen

ADRENOCEPTOR BLOCKERS

Pharmacology I

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Adrenoceptor Blockers

هذه blockers يتولوا bind على adrenoceptors وما يتولوا أي effect أو response
أو أي trigger عليه التالي ما ليس عند mediation في effect أو response

• The adrenoceptor blockers (also called **adrenergic antagonists** or **sympatholytic** agents) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects.

• These drugs act by either **reversibly** or **irreversibly** attaching to the receptor, thus preventing its activation by endogenous catecholamines.

• Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or β receptors in the peripheral nervous system.

Adrenergic antagonists $\leftrightarrow$ α β Receptors

• These drugs will **(interfere)** with the functions of the sympathetic nervous system.

نوع يمنع وخفيف، Sympathetic

← حسيات
neurotransmitter
المرتبط مع
Adrenergic
يتولوا
Sympathetic
effect

reversibly or

irreversibly

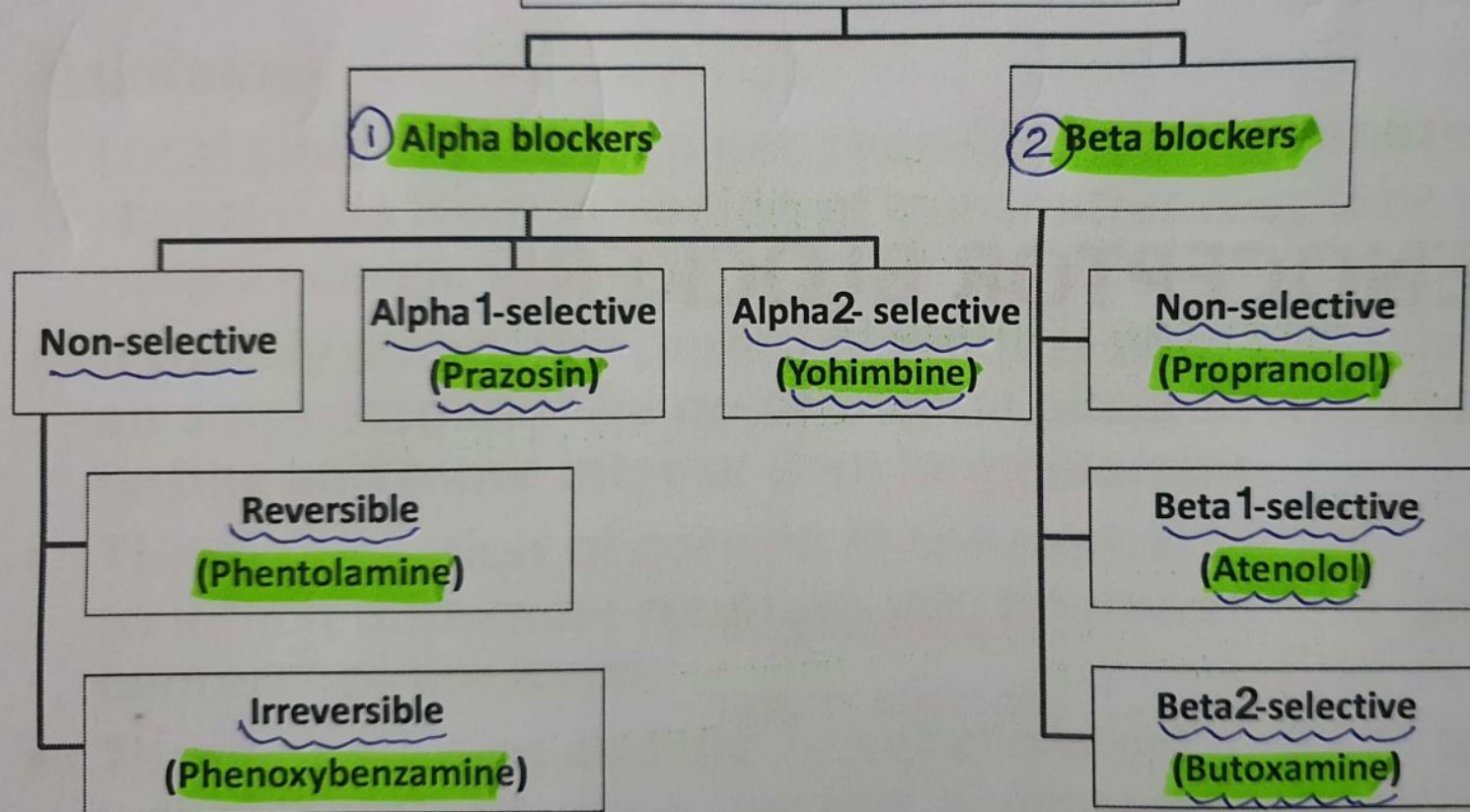
← يشتغلوا، Adrenoceptor، resaptor، ما يكون
antagonists

بالتالي هم يمنعوا المشغل تاغ، Catecholamine (وهي عبارة عن Neurotransmitter)

يتولوا Complex مع Adrenoceptor، blockers

عنا ~ ليس عند، effect

Classification of (Adrenoceptor antagonists)

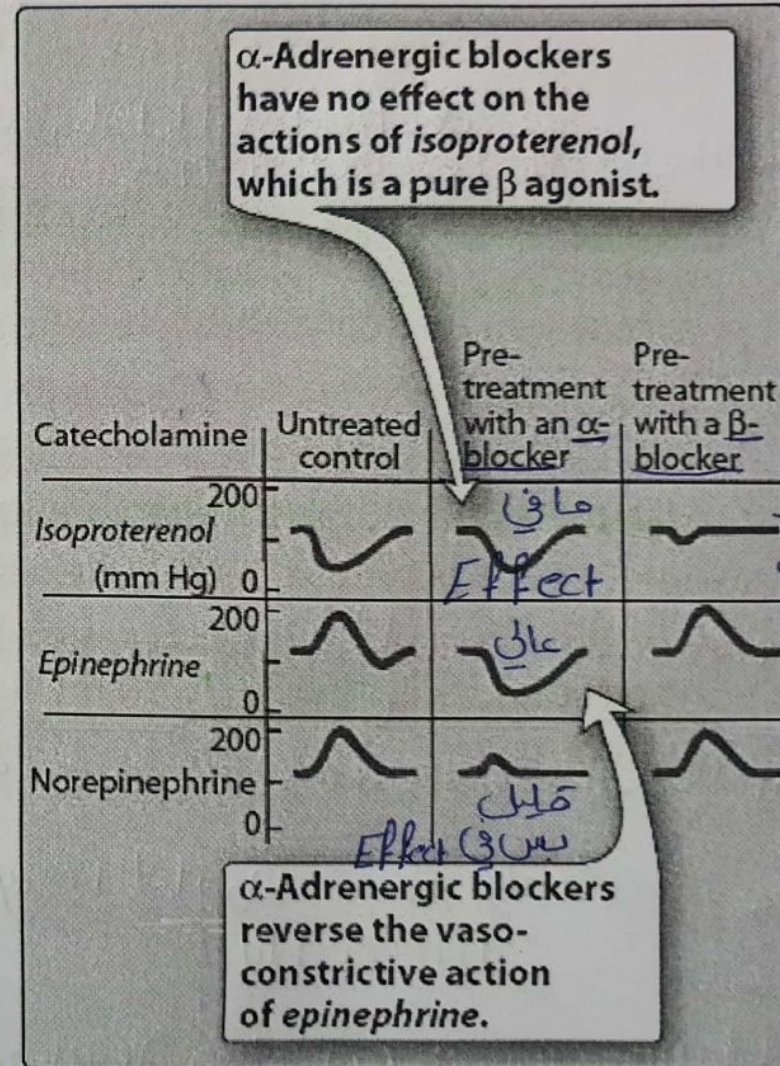


Adrenergic هون عن تأثير
blood pressure على

- Effects of adrenergic blockers on the changes in blood pressure induced by isoproterenol, epinephrine, and norepinephrine.

بغيره blood pressure mentioning بواسطة

ملكوته -
في Isoproterenol ديت Similar أكثر
لا B-blocker



(Alpha blockers)

(Pharmacokinetics)

□ Alpha-blocking drugs are all active by the oral as well as the parenteral route.

□ The duration of action of a (reversible) antagonist is dependent on the half-life of the drug in the body:

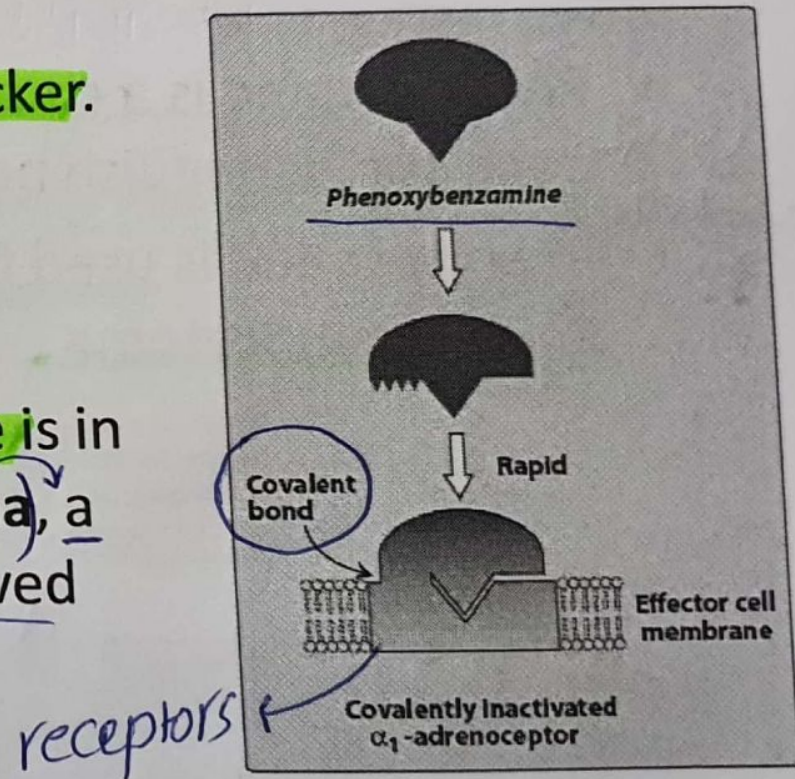
■ The shorter the half-life of the drug in the body, the less time it takes for the effects of the drug to dissipate.

□ In contrast, the effects of an (irreversible) antagonist may persist long after the drug has been cleared from the plasma. In the case of (phenoxybenzamine), the restoration of tissue responsiveness after extensive α -receptor blockade is dependent on synthesis of new receptors, which may take several days.

half life تاثيرهم يتكون اذ لم يكتمل الجزيئات لذلك
يوجدوا وقت اذ لم يكتمل الجزيئات في plasma cleared
مثال عليهم (phenoxybenzamine)
وحتى يرجع effect عندي لازم يصير تصنيع new receptor (كونه irreversible)
Phenoxybenzamine

Phenoxybenzamine

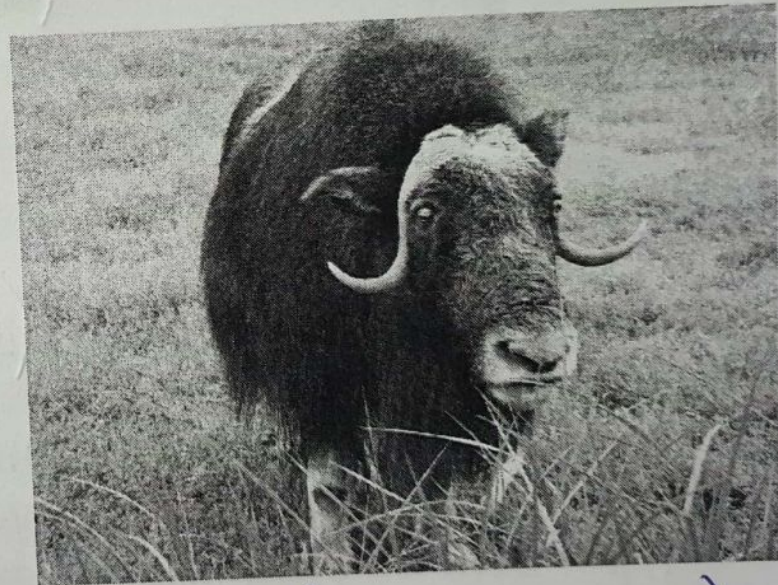
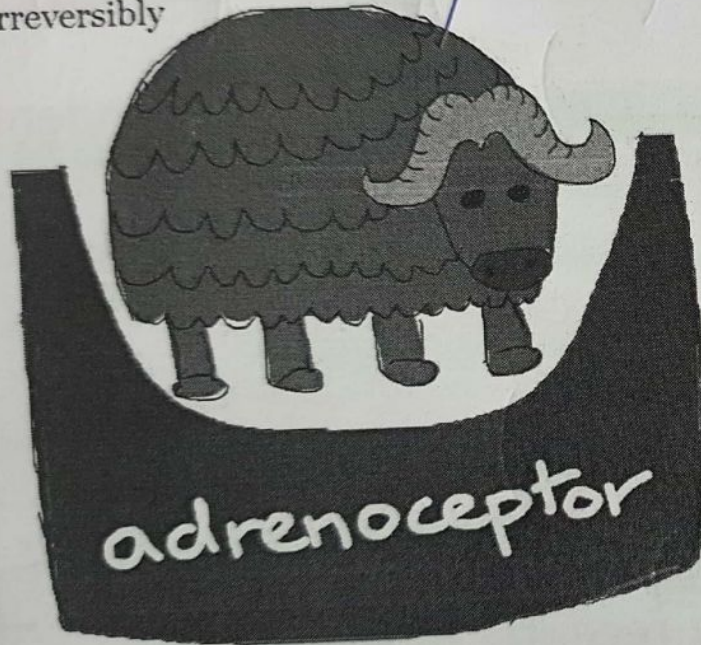
- An irreversible, long acting alpha blocker.
- It forms covalent bonds with alpha receptors, thereby inactivating the receptors
- The major use of phenoxybenzamine is in the treatment of pheochromocytoma, a catecholamine-secreting tumor derived from the adrenal medulla.



PhenOxybenzamine non-selectively block alpha receptors irreversibly

It's so heavy!

مصادره هذا الدواء :-

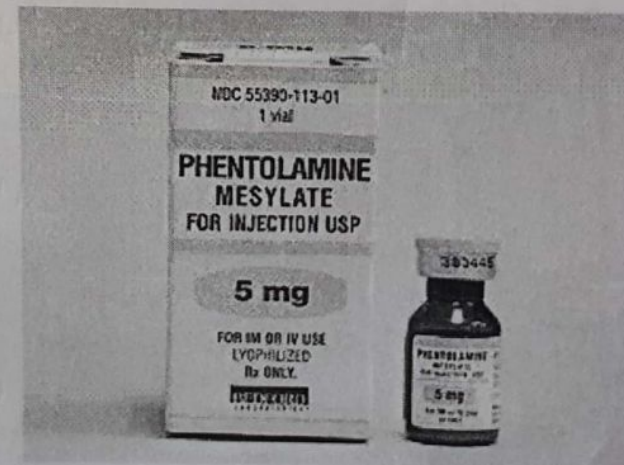


(The ox animal)

(astbleep))

Phentolamine

- Phentolamine is a competitive, reversible blocking agent that does not distinguish between α_1 - and α_2 -receptors.
non-selective ←
- Phentolamine is used for the short-term management of pheochromocytoma.



(Effects)

• Nonselective Alpha Blockers (تأثيرات عامة)

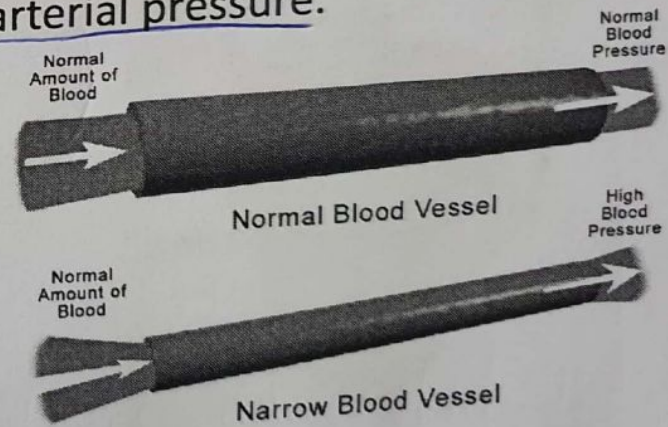
- The most important effects of nonselective blockers are those on the cardiovascular system:

– a reduction in vascular tone (vasodilation) with a reduction of both arterial and venous pressures.

– There are no significant direct cardiac effects. However, the nonselective α blockers do cause baroreceptor reflex-mediated tachycardia as a result of the drop in mean arterial pressure.

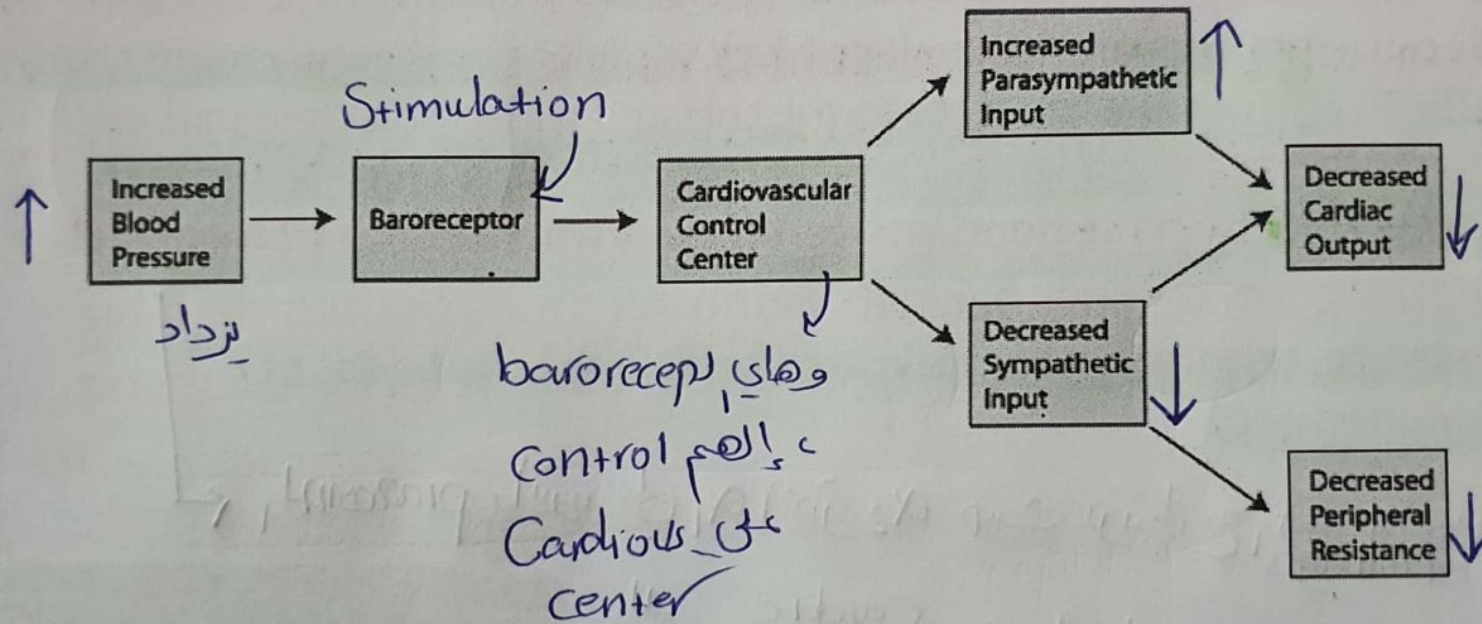
– This tachycardia may be exaggerated because the α_2 receptors on adrenergic nerve terminals in the heart, which normally reduce the net release of norepinephrine, are also blocked.

تأثيرات α_2 exaggerated تسمى tachycardia
بالتالي يقلل release نوريبيفرين



Blood Pressure Blood Flow

Baroreceptor reflex



أقلام على ALPHA 1-SELECTIVE BLOCKERS

- ☐ (Prazosin), (terazosin), (doxazosin), (tamsulosin) and (alfuzosin)
- ☐ These drugs are selective competitive blockers of the α_1 receptor.

Effects and clinical uses

□ ALPHA 1-SELECTIVE BLOCKERS

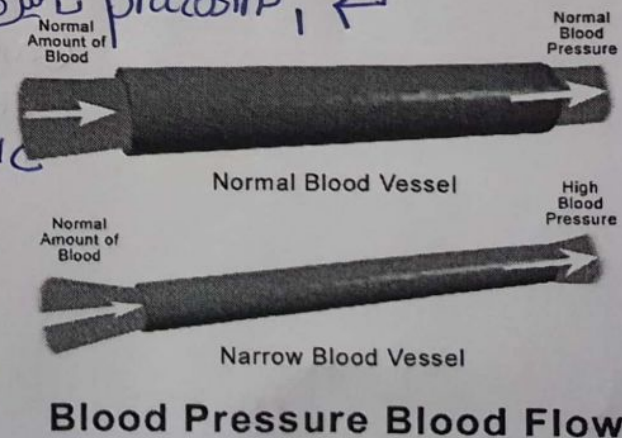
□ Because prazosin and its analogs block vascular α_1 -receptors much more effectively than the α_2 -receptors associated with cardiac sympathetic nerve endings, these drugs cause vasodilation with much less reflex tachycardia than the nonselective blockers when reducing blood pressure.

□ Prazosin, terazosin, doxazosin are useful in the treatment of (hypertension).

prazosin تأثيره على α_1 أكثر من α_2 حيث يرتبط مع α_2 nerve endings

له Cardiac Sympathetic و هذا الدواء يسبب Vasodilation

أكثر من non-selective لا يقل عني د blood pressure
(فعاليته أقوى بكثير من non-selective)

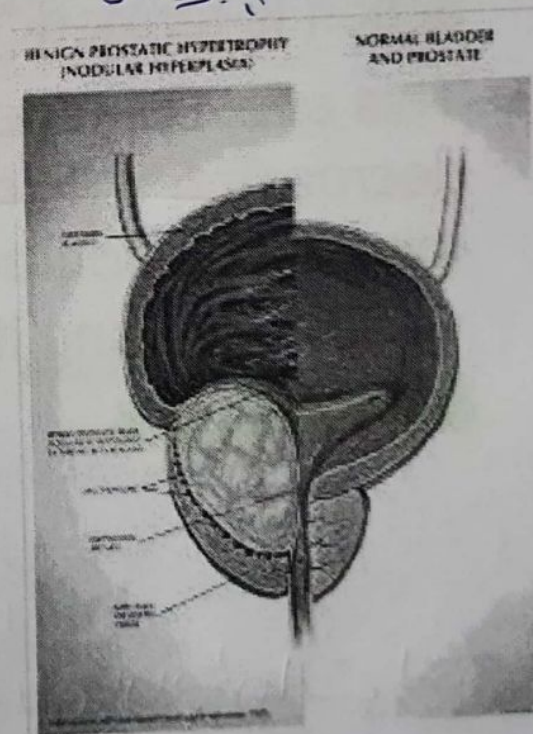
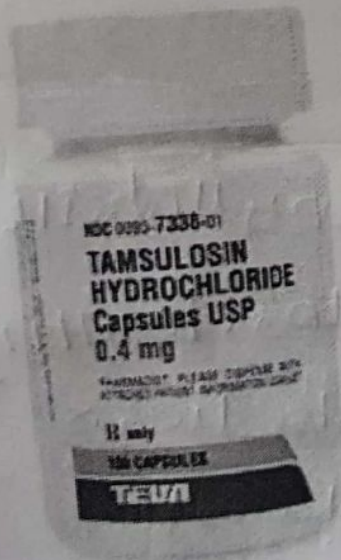


Effects and clinical uses

- ☐ ALPHA 1-SELECTIVE BLOCKERS ↓
- ☐ These drugs also relaxes smooth muscle in the bladder neck and prostate.
- ☐ Tamsulosin, and alfuzosin are used to reduce urinary hesitancy and prevent urinary retention in men with (benign prostatic hyperplasia (BPH))

(التهاب البروستات)

المقايير البروستات



Adverse effects (selective and non-selective alpha blockers)

÷ blockers Side effect

- The most important toxicities of the alpha-blockers are simple extensions of their α -blocking effects.
- The main manifestations are orthostatic hypotension.
- In the case of the nonselective agents, marked tachycardia is seen. In patients with coronary disease, angina may be precipitated by the tachycardia.

Side effect blocking α هيك خارجي

orthostatic hypotension فينبر عني

ملاحظة:
blocker يرفع ضغط الدم
agonist يخفض ضغط الدم

معلومة إضافية :- لا تعطى المريض دواء للمهبط يفضل تعطيه قبل النوم
جدة فحشية، عشاء ما يصير عندي فاكل زي نزول كبير في الضغط أثناء النوم

- The first dose of $\alpha 1$ blockers may produce an orthostatic hypotensive response that can result in syncope (fainting). This action is termed "first-dose" effect.
- This effect can be minimized by decreasing the first dose to one-third or one-fourth of the regular dose and taking it just before going to bed.



لا أعطى للمريض الدواء راح يسبالي

fainting، وهاد التي سميت first-dose

كيف نحلها في المشكلة؟

لأنه نيلش نعطى المريض جرعة صغيرة وبالتدريج لزياد الجرعات لتجنبها في المشكلة
ولا يوضع المريض في doses لأن يكون بوضعية الجلوس.

(Alpha2-selective blockers)

- Yohimbine, tolazoline are α_2 -selective competitive pharmacologic antagonists.
- Alpha 2 antagonists have relatively little (clinical usefulness).

(Beta blockers)

- Most of the effects of these drugs are due to occupation and blockade of β receptors (competitive pharmacologic antagonists).
- **Propranolol** is the prototype. (*non-selective*)
- However, some actions may be due to other effects, including partial agonist activity at β receptors and local anesthetic action, which differ among the β blockers.
- Drugs in this group are usually classified into subgroups on the basis of:
 1. β_1 selectivity
 2. Partial agonist activity
 3. Local anesthetic action
 4. Pharmacokinetic properties

$(\text{Yes} \rightarrow \alpha \text{ 1. } \underline{\text{leaves}})$

تنحصي
IV

الارقام حش حفظه (بدك تعرف مثلاً) (half life)
هل هو عالي او قليل

³Bioavailability is dose-dependent.

1. (Receptor Selectivity)

- **Propranolol**, **nadolol**, and **timolol** are typical nonselective beta blockers.
- Beta₁-receptor selectivity (β_1 block > β_2 block) is a property of **acebutolol**, **atenolol**, **esmolol**, **metoprolol**, and several other blockers. This property is an advantage when treating patients with asthma (less β_2 block, less bronchospasm). These beta₁ blockers are also called cardioselective beta blockers.
- **Labetalol** and **carvedilol** have combined α - and β -blocking actions.
- **Nebivolol** has vasodilating action mediated by nitric oxide in addition to β_1 -selective antagonism.

موجباتي اكثر شي
بالقلب

من خلال
block

لـ β_1 وحينئذ يفرغ
of relaxing factor nitric oxide

فيعبر عن
vasodilating action

1. Receptor Selectivity

- **Butoxamine** is a research drug selective for β_2 receptors.
- Selective β_2 -blocking drugs have not been actively required because there is no obvious clinical application for them (None is available for clinical use).

2. Partial Agonist Activity

• Adrenoceptor (active) و block (inactive)

- (Pindolol) and (acebutolol) have partial agonist activity.
- Partial agonist activity (also called "intrinsic sympathomimetic activity") is an advantage in treating patients with asthma because these drugs are less likely to cause bronchospasm. → effect 50% for B
- In contrast, (full antagonists) such as (propranolol) are more likely to cause severe bronchospasm in patients with airway disease.

3. Local Anesthetic Activity

- Local anesthetic activity (also called "membrane-stabilizing activity") is the result of typical local anesthetic blockade of sodium channels.
- It is unlikely that this effect is important after systemic administration of these drugs, since the concentration in plasma usually achieved by these routes is too low for the anesthetic effects to be evident.
- It is a (disadvantage) when blockers are used topically in the eye because it ① decreases protective reflexes and increases the risk of corneal ulceration. ②
- Local anesthetic effects are absent from timolol and several other blockers that are useful in glaucoma.

Local anesthetic
لأنه ما إلى anesthetic effect
بالعين eye
corneal laceration
glaucoma
تستخدمه للاستخدام
Timolol
ما يكون مع Timolol
حيلة هو يلى تستخدمه للاستخدام

4. Pharmacokinetics

- **Absorption**

- Most of the drugs in this class are well absorbed after oral administration; peak concentrations occur 1–3 hours after ingestion.

- Duration of action

- Most β antagonists have half-lives in the range of 3–10 hours. A major exception is **esmolol**, which is a short-acting ester blocker that is used only parenterally and has a half-life of approximately 10 minutes.

Bioavailability = 0 Esmolol

والبيوavailability، كتي الحسب
parenteral

Esmolol	10 min
Acebutolol	3–4 hr
Pindolol	3–4 hr
Metoprolol	3–4 hr
Propranolol	4–6 hr
Timolol	4–6 hr
Labetalol	4–6 hr
Carvedilol	7–10 hr
Nebivolol	10–30 hr
Nadolol	14–24 hr

4. Pharmacokinetics

- **Bioavailability**

- **Propranolol** undergoes extensive hepatic (first-pass) metabolism; its bioavailability is relatively low.

□ A major consequence of the low bioavailability of propranolol is that oral administration of the drug leads to much lower drug concentrations than are achieved after intravenous injection of the same dose. *يعني عن طريق الوريد*

- For the same reason, bioavailability is limited to varying degrees for most β antagonists with the exception of **betaxolol**, **penbutolol**, **pindolol**, and **sotalol**.

- **Distribution**

- The β antagonists are rapidly distributed and have large volumes of distribution. **Propranolol** and **penbutolol** are quite lipophilic and readily cross the blood-brain barrier.

→ Can cross easily

4. Pharmacokinetics

- (Clearance) agent + $\downarrow$ metabolism (hepatic blood flow) $\downarrow$ (أي ظل بالوريد في (hepatic blood flow) يأت على (metabolism) لا ي
- **Clearance**
 - Most beta agonists are metabolized by hepatic enzymes.
 - The elimination of these drugs such as propranolol may be prolonged in the presence of liver disease, diminished hepatic blood flow, or hepatic enzyme inhibition. $\uparrow$ هذه الحالة بشكل مطول بالوريد
 - **Nadolol** is excreted unchanged in the urine and has the longest half-life of any available β antagonist (up to 24 hours). The half-life of nadolol is prolonged in renal failure.

يطاوعت
الوريد
urine

في
urine

prolongation Half life

إذا كان عدي مشكلة بالوريد (لأنه يصير له

renal failure

Beta Blockers

Effects and clinical uses

1. Hypertension
2. Coronary artery diseases
3. Cardiac arrhythmias
4. Heart failure
5. Glaucoma
6. Hyperthyroidism
7. Neurological conditions

Hypertension



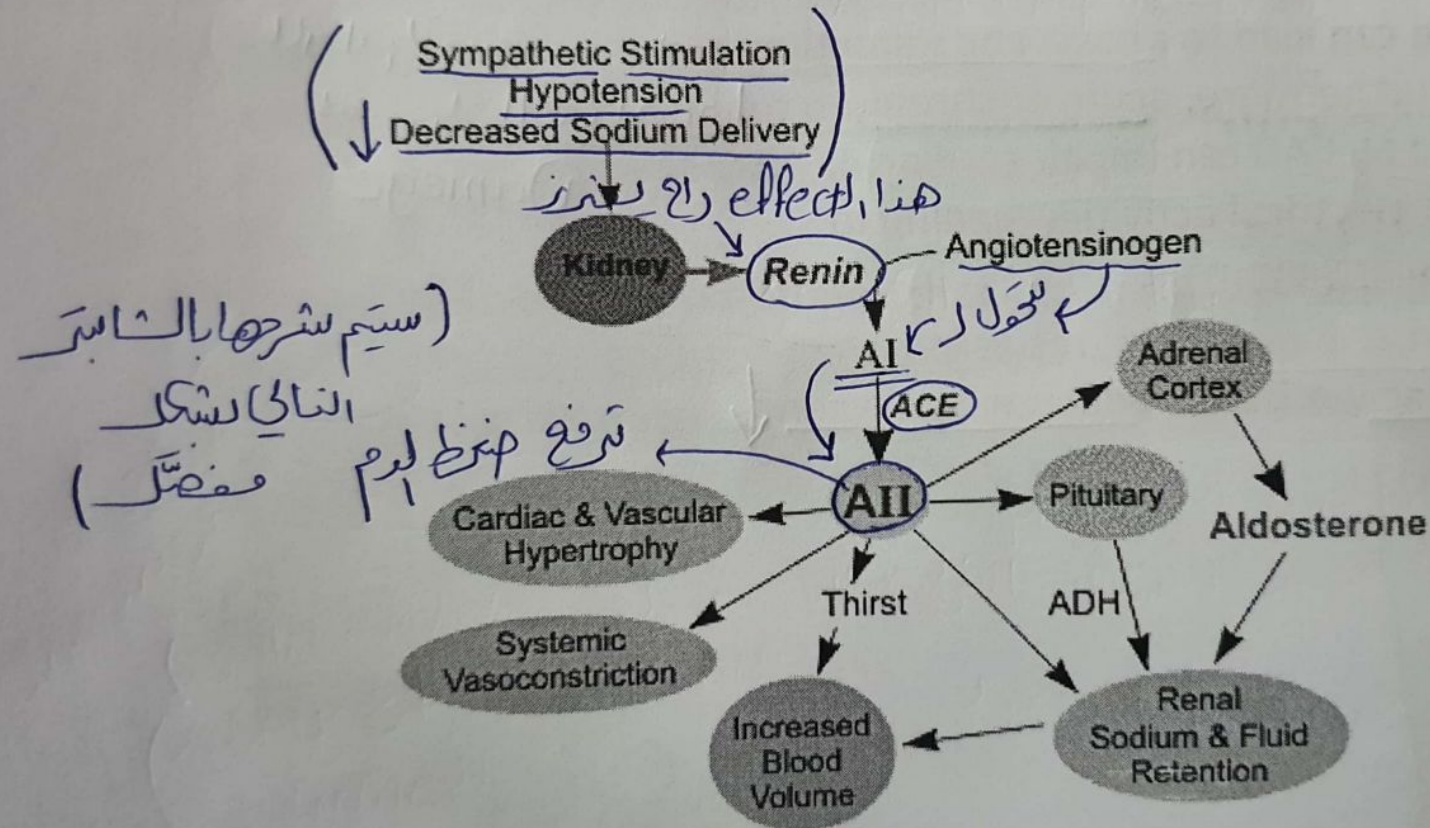
* بتعطيل beta blocking drug بشكل chronicallly

- Beta-blocking drugs given chronically lower blood pressure in patients with hypertension.
- The mechanisms involved are not fully understood but probably include reduction in cardiac output, suppression of renin release and effects in the central nervous system.
- These drugs do not usually cause hypotension in healthy individuals with normal blood pressure.
- No postural hypotension occurs, because the α_1 -adrenergic receptors that control vascular resistance are unaffected.

لا يسببوا hypotension (لا يحدث)

التي لها effect

Renin-Angiotensin system



(فيسولوجي)

Coronary artery diseases (CAD)

- **Coronary artery disease (CAD)** also known as **coronary heart disease**, or **ischemic heart disease (IHD)**.

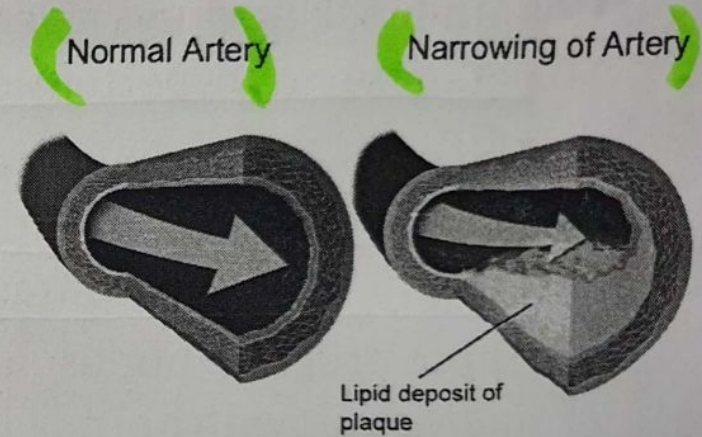
(تضييق في الشرايين)

- When CAD restricts blood flow to the myocardium (ischemia) there is an imbalance between oxygen supply and oxygen demand.

حالة عدم توازن

بين الأكسجين الداخل والخارج

When the oxygen supply is insufficient to meet the oxygen demand, the myocardium becomes hypoxic. This is often associated with chest pain (angina) and other clinical symptoms.



Coronary Artery Disease

Coronary artery diseases (CAD)

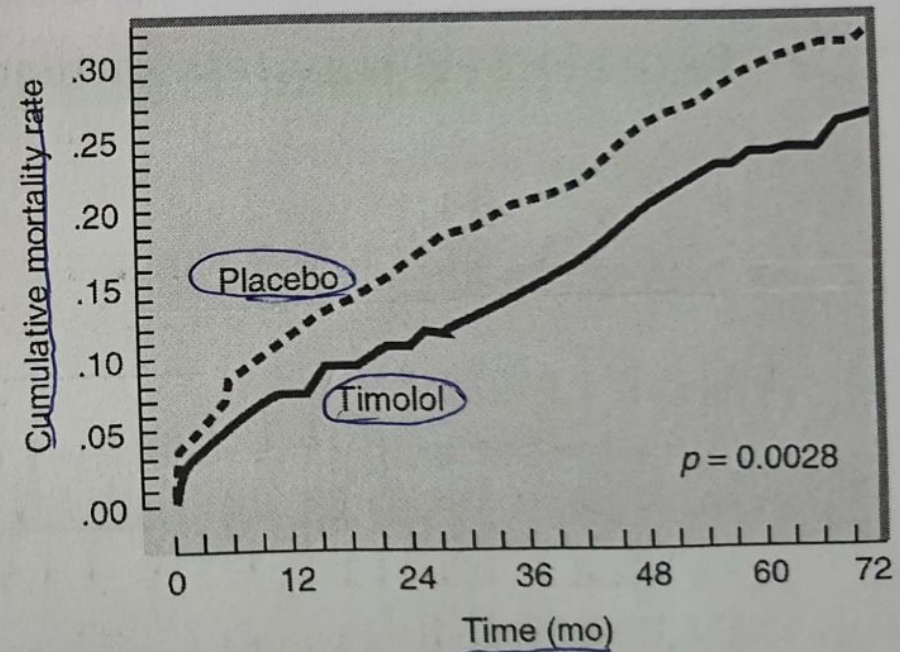
- Severe ischemia can lead to anoxia and infarction of the tissue. Furthermore, acute or chronic ischemia caused by CAD can impair cardiac mechanical and electrical activities leading to heart failure and arrhythmias.
المرحلة الأخيرة
تؤدي إلى
تسبب cell يضرها
Damage
- Blockade of cardiac β receptors, result in decreased cardiac work and reduction in oxygen demand.
يؤدي صوت
↓



Coronary artery diseases (CAD)

- Beta blockers are very valuable in the treatment of angina, chronic heart failure and following myocardial infarction.
 - Long-term use of timolol, propranolol, or metoprolol in patients who have had a myocardial infarction prolongs survival.

يُطيل من البقاء
على قيد الحياة

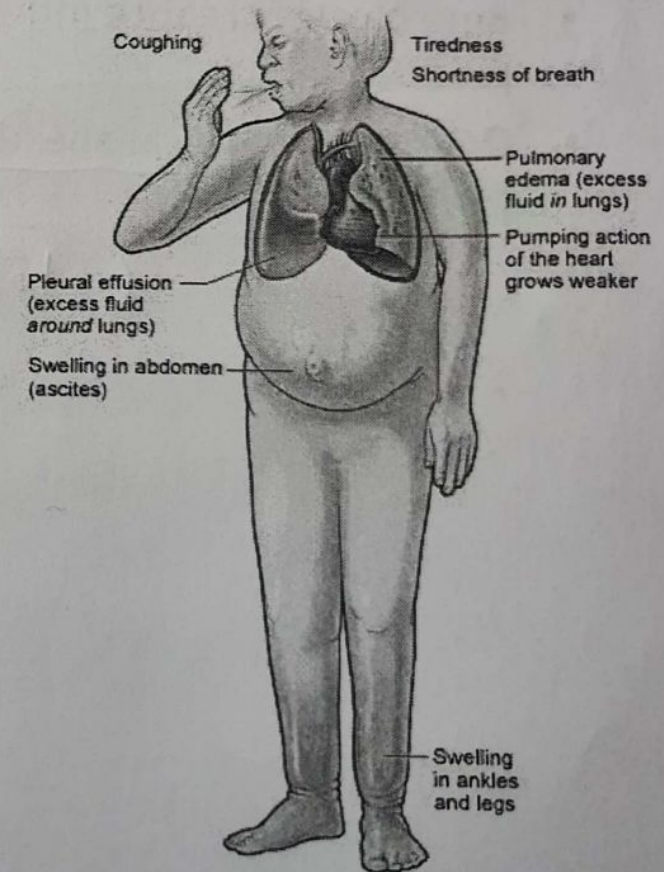


Coronary artery diseases (CAD)

عذلة القلب يكون فيها مشكلة، بحيث الدم تكون

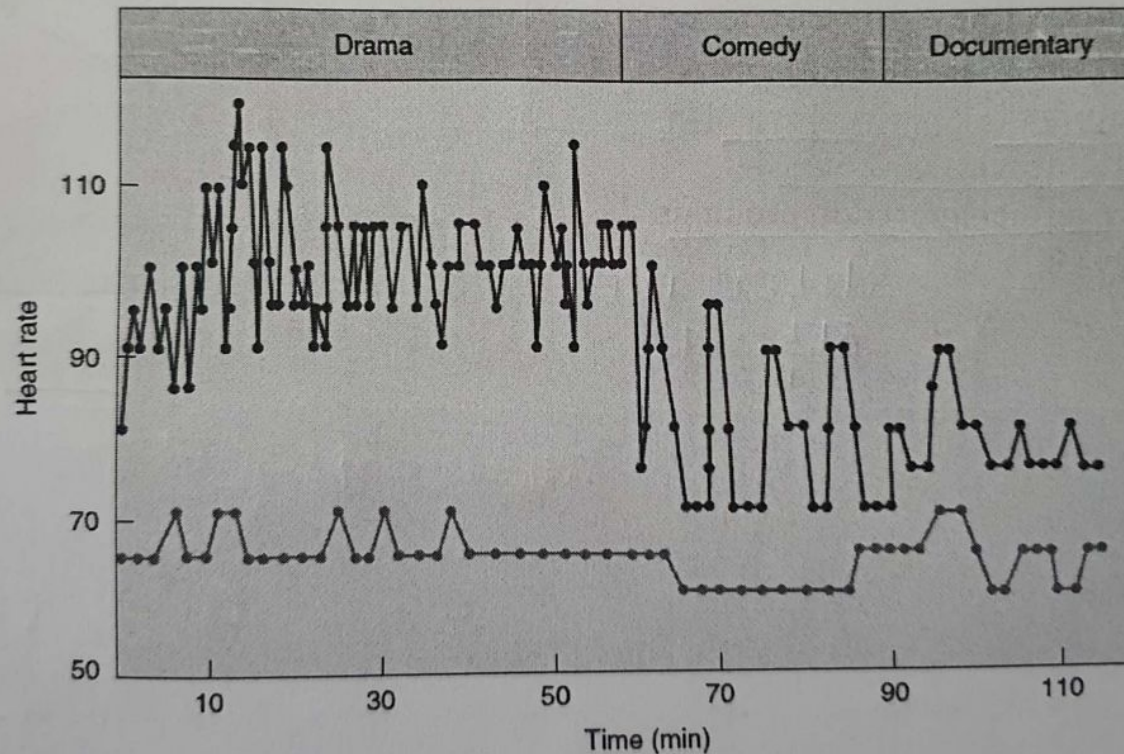
أقل من الطبيعي (الدم المنقولا)
Heart failure occurs when the heart is unable to provide sufficient pump action to maintain blood flow to meet the needs of the body.

- Clinical trials have demonstrated that at least three β antagonists—**metoprolol**, **bisoprolol**, and **carvedilol**—are effective in reducing mortality in selected patients with chronic heart failure.



Cardiac arrhythmias

- Beta blockers suppress cardiac arrhythmias



Glaucoma

- Beta blockers reduce intraocular pressure by decreasing aqueous humor production.
- Ones that lack (local anesthetic activity) are useful for this indication. i.e. timolol.

(مکینا عها قبل)

Hyperthyroidism

hyperthyroidism بالمرتبط مع

نستخدم β blockers مثل لعلاج هذا المرض، لئلا يؤثر على

- **Hyperthyroidism**, often referred to as an **overactive thyroid**, is a condition in which the thyroid gland produces and secretes excessive amounts of thyroid hormones, **triiodothyronine (T3)** and/or **thyroxine (T4)**.

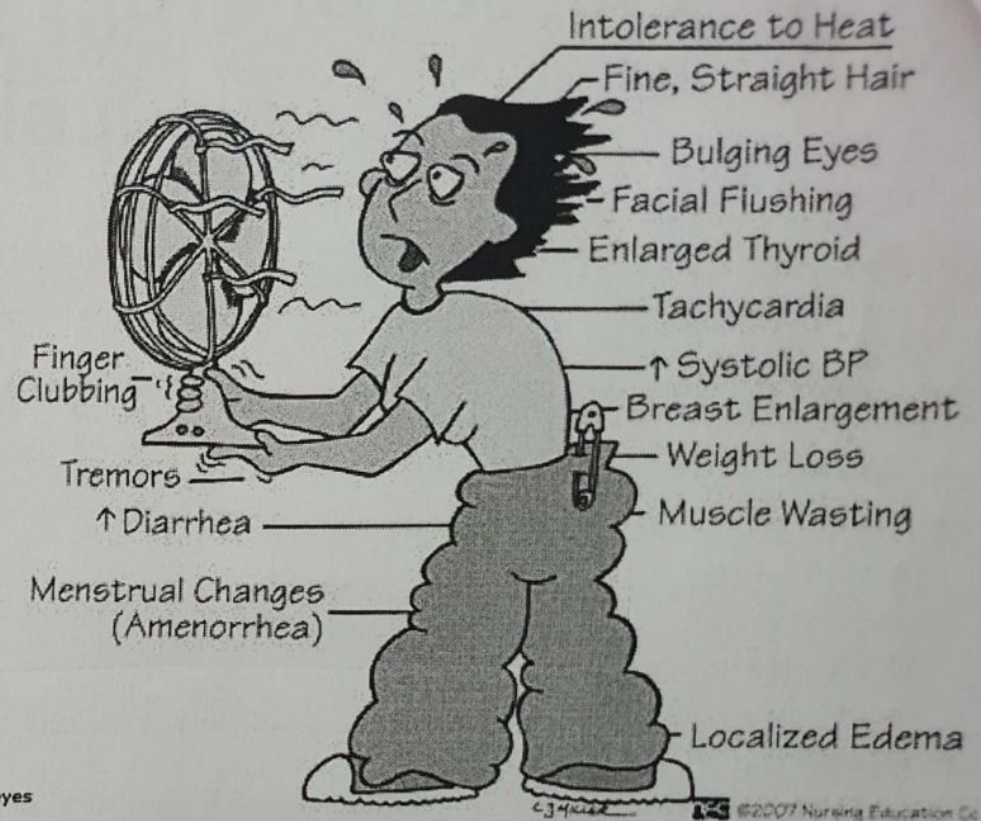
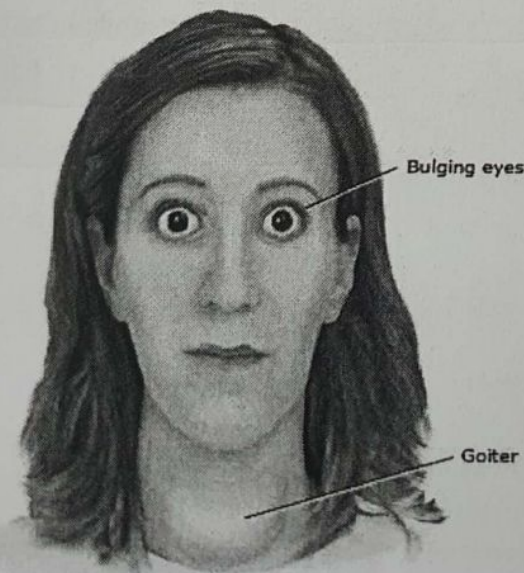
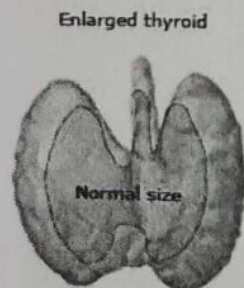
- The most common symptoms are associated with adrenergic stimulation: tachycardiac, palpitations, nervousness, tremor, and increased blood pressure.

يعني، β blockers نستخدم

ليأثر على symptoms، بالمرتبط مع Hyperthyroidism

HYPERTHYROIDISM

الاعمال الصالحة



Einige goldene Metallgegenstände, Blocken, die eine

لحرقن اوعيد يلي blocked β ما يشتغل فيه الحالة، انا مع امانة
دعاء ثاني.

(Hyperthyroidism)

معناش اول
Symptoms فقط
مش لل hyperthyroidism

- The effects β antagonists relate to blockade of adrenoceptors and perhaps to the inhibition of peripheral conversion of thyroxine to triiodothyronine.
- During the acute phase of thyrotoxicosis, β -adrenoceptor-blocking agents without intrinsic sympathomimetic activity are extremely helpful.

مع β
أشلة على
أدوية
مستحبة ؟

Propranolol, 20–40 mg orally every 6 hours, or **metoprolol**, 25–50 mg orally every 6–8 hours, will control tachycardia, hypertension, and atrial fibrillation.

Neurological conditions

- **Migraine**
 - **Propranolol** reduces the frequency and intensity of migraine headache . Other β -receptor antagonists with preventive efficacy include **metoprolol**, **atenolol**, **timolol**, and **nadolol**. The mechanism is not known.
- Reduce certain **tremors**.
 - The somatic manifestations of anxiety may respond dramatically to low doses of propranolol, particularly when taken prophylactically.
 - For example, benefit has been found in **performance anxiety** ("stage fright").
- **Propranolol** may contribute to the symptomatic treatment of alcohol withdrawal in some patients.

Adverse effects of beta blockers

- (**Bradycardia**) is the most common adverse cardiac effect of β -blocking drugs.
← حائض عندي مريض على β و فجأة يوقف لرواد
- **Arrhythmias**
(الما توقف لرواد) (نزل الجهد / نزل الكوي)
- Treatment with β blockers must never be stopped quickly because of the risk of precipitating cardiac arrhythmias, which may be severe.
- The β blockers must be tapered off gradually for at least a few weeks.
- Because long-term treatment with a β antagonist leads to up-regulation of the β receptor. On suspension of therapy, the increased receptors can worsen angina or hypertension.

Adverse effects of beta blockers

non-selective B-blockers
من غير انتقائية بيتا بلاكرز

- **Bronchoconstriction**
- Beta 2-receptor blockade associated with the use of nonselective agents commonly causes worsening of preexisting asthma and other forms of airway obstruction without having these consequences in normal individuals. Nonselective beta blockers are contraindicated in patients with asthma or COPD.
- While β 1-selective drugs may have less effect on airways than nonselective β antagonists, they must be used very cautiously in patients with reactive airway disease.

Adverse effects of beta blockers

- Disturbances in glucose metabolism

- β Blockade leads to decreased glycogenolysis and decreased glucagon secretion.

تقللوا الجلوكون بالجسم

- Therefore, if a patient with type 1 diabetes is to be given propranolol, very careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after insulin injection.

انخفاض
نزول

السكوي

- This is of special importance because the normal physiologic response to hypoglycemia (tachycardia, tremor, and anxiety) may be masked by β blockers.

المريض المصاب بالسكوي، لازم نراقبهم monitoring لمستوى الجلوكون بالدم، أو نعطهم β

selective

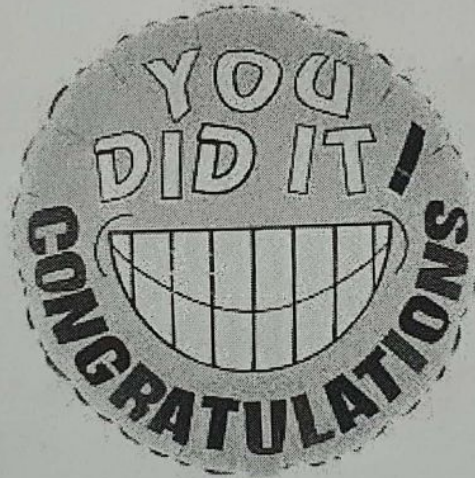
كيف يعرف المريض انه اسكوي نزل عنده ؟

إذا احارجه (tachycardia, tremor) and anxiety

(Adverse effects of beta blockers)

- (CNS effects)
- Propranolol and highly lipid soluble beta blockers may have numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, vivid dreams (including nightmares), decreased performance, and depression manifested by insomnia.

relief



THAT'S THE END OF THIS CHAPTER

Academy.

by : Hawazen Abdallah