B-blockers

Effects not related to Beta-Blockade

- It has been suggested that some intrinsic sympathomimetic activity is desirable to prevent untoward effects such as asthma or excessive bradycardia.
- Pindolol and some other ß blockers are partial agonists.
- They [partial agonists^^^] may be useful in patients who develop symptomatic bradycardia or bronchoconstriction in response to pure antagonist β-adrenoceptor drugs.
- Some β blockers have local anesthetic effect "membrane-stabilizing effect" … however, the anesthetic effect isn't so evident because when we give these drugs orally or IV, the concentration in the plasma would be low to make a significant local anesthetic effect. we must not give β-blockers with local anesthetic effect for patients who have glaucoma.

Sotalol

- it's a non-selective ß-receptor antagonist that lacks local anesthetic action
- it can block both ß receptors + potassium channels
- it's used to treat ventricular & supraventricular arrhythmias.

Specific Agents

1. propranolol

- it's the first drug discovered , in the past they used it to treat the angina, but later they noticed that it decreases the blood pressure so they used it for patients with hypertension .. and then its other uses came gradually
- it's the prototypical β-blocking drug.
- **It has low bioavailability ( a disadvantage ) , but we increase the bioavailability by increasing the dose ,why? Because by increasing the dose the hepatic enzymes are saturated → we get better bioavailability**
A long-acting form of propranolol is available; prolonged absorption of the drug may occur over a 24-hour period (the dose covers the whole day).

- It can block serotonin receptors in the brain, though the clinical significance is unclear.
- Has no partial agonist action at β receptors.

**2. Metoprolol, Atenolol**

- Are β1–selective antagonists. But by increasing the dose they lose the selectivity.
- What's the difference between the two? Atenolol is given once a day because it has a longer half-life, while metoprolol is given three times a day "has shorter half life", but both are good for people with bronchial asthma "coz of their selectivity".
- Actually their β1 selectivity is modest; so they should be used with great caution in patients with a history of asthma. But in selected patients with chronic obstructive lung disease the benefits may exceed the risks (like in patients with myocardial infarction, β blockers prolong their survival).
- If we give diabetic patients non-selective β blockers they might have hypoglycemic shock! But if necessary to give them β blocker, we choose a selective β1 blocker.
- Also, in peripheral vascular disease (where people have defects in the peripheral circulation, and if they walk they'll feel tired immediately and their legs will become blue in color due to obstructions in the vessels) we use selective β1 blockers.

**3. Nebivolol**

- One of the new drugs "so it's expensive"
- It's the most highly selective β1-adrenergic receptor blocker.
- It has the additional quality of eliciting vasodilation, maybe due to stimulation of the endothelial nitric oxide (which is a very powerful vasodilator).

**4. Nadolol**

- A very long acting drug → one pill a day is enough.
- Its spectrum of action is similar to that of timolol.
5. Timolol

- It's nonselective
- It's the best β blocker for ocular use " used for glaucoma"
- It's given twice a day and good to control glaucoma

6. Pindolol, acebutolol, celiprolol

- They have partial β-agonist activity; means that they block β receptors and at the same time they can cause stimulation which is a good thing!
- They are effective in hypertension and angina and may be less likely to cause bradycardia and abnormalities in plasma lipids than other β antagonist.

- **Pindolol**
  - Is partial β agonist
  - Has an action on serotonin signaling " it increases the serotonin firing rate which is good for patients with hypertension or depression "

![Depression Can be:](Image)

**Endogenous**
There’s no actual cause “the person has every thing” ... here the person has low levels of serotonin or norepinephrine

**Exogenous**
Comes because of failing in anything .. Like fail in an exam

- **Celiprolol**
  - is a β1-selective antagonist
  - has modest capacity to activate β2 receptors so it's good for people with bronchial asthma
what do we mean by partial agonist??

Well, the full agonist gives the maximum response .. and the partial agonist has a ceiling "not full response"

7. Labetalol

- Has 4 isomers … there's 2 asymmetric carbon atoms
  So there's 4 isomers (each carbon atom has a mirror image) \[2^2\]
  Two of these isomers have to effect at all, and the other two has effect. One of them blocks alpha1 receptors "like prazosin", and the other one has nonselective β blocker with partial agonist activity “like pindolol” It's used in the emergency cases, when there's somebody with hypertension ; he's given labetalol in the ICU to decrease his pressure immediately
- Hypotension induced by labetalol is accompanied by less tachycardia (why? Coz it's a β-blocker) than occurs with phentolamine and similar alpha blockers.

8. Carvedilol

- Nonselective β-receptor antagonist ,, but also has α1 blocking effect
  So it's more potent β-blocker than α-blocker
- The ratio of α1 to β receptor antagonist potency for carvedilol is approximately 1:10
- Has a half-life of 6-8 hours
- They discovered that it prolongs the survival of heart failure patients

9. Esmolol

- It's very short-acting β-blocker
- It's an ester ; so it undergoes breakdown by the esterase in the plasma.. so its half-life doesn't exceed 10min , and that's why we give it in continuous intravenous infusion —> so it reaches the steady-state concentrations quickly and the actions of the drug are terminated rapidly when its infusion is discontinued.. so it's used only in hospitals in emergency units to stop the arrhythmia [during the surgery]
- when we notice that the dose has increased we stop the infusion

- Esmolol is useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis (excess thyroid release), perioperative hypertension, and myocardial ischemia in acutely ill patients

**Clinical pharmacology of the β-receptor-blocking drugs**

- **Hypertension**: before almost 20-30 years, β-blockers were number 1 in treating hypertension, and they don't have bad side effects. In the past they used reserpine …. I'm not sure 😃 but they realized later that it makes depletion for the catecholamines (epinephrine, norepinephrine, dopamine) which leads to acute depression, and also it cause ulcer and diarrhea.

- β-blocker drugs are often used with either a diuretic [sometimes given with drugs to enhance their performance] or a vasodilator

- These drugs may be administered once or twice

- They're less effective in elderly and in African ancestry (black race) ... why? Coz they have some genetic differences

- **Ischemic heart disease**: those patients have narrow vessels. Actually, vessels are elastic that's why we can feel the pulse, but in elderly people they lose their elasticity so we can't feel their pulse properly … these patients in rest state have enough blood supply, but if they become angry, sad or if they do any effort → the sympathetic activity will increase → the heart rate and the blood flow to it will increase but the coronary arteries are not elastic enough to be consistent with increased blood flow so they'll have chest pain and angina which will trigger a fatal arrhythmias

So the β – blockers are very good to prevent angina pain by slowing the heart rate (slowing its contractility)

- Multiple large-scale prospective studies indicate that the long-term use of timolol, propranolol, or metoprolol in patients who have had a myocardial infarction prolongs survival

- β-adrenoceptor antagonists are strongly indicated in the acute phase of a myocardial infarction
• contraindications include bradycardia, hypotension, moderate or severe left ventricular failure, shock, heart block, and active airways disease

❖ **cardiac arrhythmias:** the arrhythmia might be because of the atrium or the ventricle, but we're concerned about the ventricle. So β-blockers are useful here specially if the arrhythmia is precipitated by catecholamines (3shan el-action potential ma tnzal 3la el-ventricle w bettale bn7meeh.. the ventricles are very important in blood pumping..3ashan hek ben5af 3lehoom 😊)

• by increasing the atrioventricular nodal refractory period, β-antagonists slow ventricular response rates in atrial flutter and fibrillation.
• These drugs can also reduce ventricular ectopic beats, particularly if the ectopic activity has been precipitated by caticholamines
• Sotalol has antiarrhythmic effects involving ion channel blockade in addition to its β-blocking action

❖ **Heart failure:** in the past they didn’t recommend β-blockers for those patients but then they realized that careful use of β-blockers prolongs survival, so it’s effective in reducing mortality in selected patients with chronic heart failure.

Here when we give β blocker we use smallest possible dose and every 2-3 weeks we increase the dose a little bit. Although the mechanisms are uncertain, there appear to be beneficial effects on myocardial remodeling and in decreasing the risk of sudden death.

❖ **Glaucoma:** here the best drug could be used is timolol, also we can use any other β-blocker (not necessary to have a local anesthetic effect).

• They found that timolol having efficacy comparable with epinephrine or pilocarpine and it doesn't interfere with vision
• What we are afraid of; is timolol absorption from the eye in patients with heart problems because it will affect them.
Hyperthyroidism:
- People with hyperthyroidism have excessive secretions thyroid hormones (there's 2 hormones: tetraiodothyronine [thyroxine] & triiodothyronine "the last is the active form")
- The β antagonists are beneficial in this condition. The effects presumably relate to blockade of adrenoceptors and perhaps in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine.
- Nowadays, they use radioactive iodine which cause some destruction in the thyroid gland
- Propranolol has been used extensively in patients with thyroid storm (severe hyperthyroidism); it's used cautiously in patients with this condition to control supraventricular tachycardias that often lead to heart failure

Neurologic diseases:
- Propranolol reduces the frequency and intensity of migraine headache. Other β-receptor antagonists with preventive efficacy include metoprolol, atenolol, timolol and nadolol.
- The somatic manifestations of anxiety may respond to low doses of propranolol particularly when taken prophylactically. It has benefit with performance anxiety "stage fright".
- Propranolol may contribute to the symptomatic treatment of alcohol withdrawal in some patients

Clinical toxicity of the beta-receptor antagonist drugs
- Bradycardia is the most common adverse cardiac effect of β-blocking drugs
- Sometimes patients note coolness of hands and feet in winter
- Central nervous system effects include mild sedation, vivid dreams, and rarely, depression
- Beta2-receptor blockade associated with the use of nonselective agents commonly causes worsening of preexisting asthma and other forms of airway obstruction
- 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
- Beta1-selective antagonists are generally well tolerated in patients with mild to moderate peripheral vascular disease, but caution is required
in patients with severe peripheral vascular disease (we said that using nonselective drugs would make the case worse)

- Caution must be exercised in starting a $\beta$-receptor antagonist in patients with compensated heart failure even though long-term use may prolong life
- A very small dose of a $\beta$ antagonist may provoke severe cardiac failure in a susceptible individual
- Beta blockers may interact with the calcium antagonist verapamil causing bradycardia, heart failure, and cardiac conduction abnormalities. These adverse effects may even arise in susceptible patients taking a topical $\beta$ blocker and oral verapamil
- Patients with ischemic heart disease or hypertension may be at increased risk if $\beta$ blockade is suddenly interrupted. This might involve up-regulation of $\beta$ receptors
- It is inadvisable to use $\beta$ antagonists in insulin-dependent diabetic patients who are subject to frequent hypoglycemic reactions. Beta1-selective antagonists offer some advantage in these patients